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I, JONNE YABSLEY, TEAM LEADER EXAMINATION SUPPORT AND SALES hereby certify that annexed is a true copy of the Provisional specification in connection with Application No. 2002953223 for a patent by THE CORPORATION OF THE TRUSTEES OF THE ORDER OF THE SISTERS OF MERCY IN QUEENSLAND as filed on 06 December 2002.

WITNESS my hand this
Twenty-third day of December 2003

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Regulation 3.2

The Corporation of the Trustees of the
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AUSTRALIA

Patents Act 1990

PROVISIONAL SPECIFICATION

for the invention entitled:

"Novel Therapeutic Molecules and Uses Thereof"

The invention is described in the following statement:

NOVEL THERAPEUTIC MOLECULES AND USES THEREOF

FIELD OF THE INVENTION

The present invention relates generally to a novel lectin receptor and to derivatives, homologues, analogues, chemical equivalents and mimetics thereof and, more particularly, to novel splice variants of DEC-205. The present invention further relates to a novel lectin and to derivatives, homologues, analogues, chemical equivalents and mimetics thereof and, more particularly, to a novel type I C-type lectin, herein referred to as "DCL-1". The present invention also contemplates genetic sequences encoding said novel molecules and derivatives, homologues and analogues thereof. The molecules of the present invention are useful in a range of therapeutic, prophylactic and diagnostic applications.

BACKGROUND OF THE INVENTION

Bibliographic details of the publications referred to numerically in this specification are collected at the end of the description.

The reference to any prior art in this specification is not, and should not be taken as, an acknowledgment or any form of suggestion that that prior art forms part of the common general knowledge in Australia.

Hodgkin's disease accounts for 15% of all lymphomas, but less than 1% of all cancers. It is diagnosed in 7 per 100,000 people annually. Hodgkin's disease can occur at any age, but is rare in children. It most commonly strikes young adults between the ages of 20-30 years and adults above the age of 50 years. Hodgkin's disease is more common in higher-socio-economic groups and more men are affected by the illness than women.

Hodgkin's disease is characterised by the presence of Reed-Sternberg cells. These are malignant morphologically distinct cells, the presence of which is used as a diagnostic criterion of Hodgkin's disease.

In nodular lymphocyte predominant Hodgkin's disease, Hodgkin and Reed-Sternberg cells occur amongst a background of polyclonal B and T cells. The proliferation of these lymphocytes is postulated to be mediated by malignant Hodgkin and Reed-Sternberg cells. Hodgkin and Reed-Sternberg cells exhibit characteristics in common with antigen presenting cells such as activated B cells and dendritic cells. For example, Hodgkin and Reed-Sternberg cells lines, such as KM-H2, L428 and HDLM-2, express cell surface molecules required for costimulation/proliferation of B and T cells (MHC class II, CD40, CD80 and CD86), cell adhesion molecules involved in APC-T cell interactions (LFA-1, CD11c, ICAM-1-3), and produce inflammatory cytokines (TNF-α and lymphotoxin) and non-inflammatory cytokines (e.g. CSF-1, IL-5 and IL-13), all of which may contribute to the pathology of Hodgkin's disease.

In light of the unique distribution and characteristics of Reed-Sternberg cells, there is an on-going need to investigate and define the phenotypic and functional characteristics of this population of cells.

In work leading up to the present invention, the inventors have studied the cell surface molecule expression of Reed-Sternberg cells with a view to identifying molecules which may provide useful immunotherapeutic targets. In this regard, the inventors have surprisingly identified novel alternatively spliced DEC-205 mRNAs which encode the intact DEC-205 ectodomain plus a unique sequence encoding for an additional carbohydrate recognition domain (CRD), a transmembrane domain and a cytoplasmic domain derived from a newly identified type I C-type lectin termed DCL-1.

SUMMARY OF THE INVENTION

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

The reference to any prior art in this specification is not, and should not be taken as, an acknowledgment or any form of suggestion that that prior art forms part of the common general knowledge in Australia.

The subject specification contains nucleotide sequence information prepared using the programme PatentIn Version 3.1, presented herein after the bibliography. Each nucleotide sequence is identified in the sequence listing by the numeric indicator <201> followed by the sequence identifier (eg. <210>1, <210>2, etc). The length, type of sequence (DNA, etc) and source organism for each nucleotide sequence is indicated by information provided in the numeric indicator fields <211>, <212> and <213>, respectively. Nucleotide sequences referred to in the specification are identified by the indicator SEQ ID NO: followed by the sequence identifier (eg. SEQ ID NO:1, SEQ ID NO:2, etc.). The sequence identifier referred to in the specification correlates to the information provided in numeric indicator field <400> in the sequence listing, which is followed by the sequence identifier (eg. <400>1, <400>2, etc). That is SEQ ID NO:1 as detailed in the specification correlates to the sequence indicated as <400>1 in the sequence listing. A summary of the sequences detailed in this specification are provided immediately prior to the examples, in Table 4.

One aspect of the present invention provides a novel nucleic acid molecule in isolated form wherein said nucleic acid molecule comprises a novel DEC-205 intergenic splice variant.

In another aspect there is provided a novel nucleic acid molecule in isolated form wherein said nucleic acid molecule comprises a DEC-205/DCL-1 intergenic splice variant.

Yet another aspect provides a nucleic acid molecule or derivative, homologue or analogue thereof comprising a nucleotide sequence encoding an amino acid sequence substantially as set forth in SEQ ID NO:2 or SEQ ID NO:21 or a derivative, homologue or mimetic thereof having at least about 45% or greater similarity to at least 30 contiguous amino acids in SEQ ID NO:2 or SEQ ID NO:21.

Still another aspect provides a novel nucleic acid molecule or a derivative, homologue or analogue thereof in isolated form comprising a nucleotide sequence substantially as set forth in SEQ ID NO:1 or SEQ ID NO:20 or a nucleotide sequence having at least about 50% similarity to all or part thereof or a nucleotide sequence capable of hybridising to the sequence set forth in SEQ ID NO:1 or SEQ ID NO:20 under low stringency conditions at 42°C.

Yet still another aspect of the present invention contemplates a nucleic acid molecule or derivative, homologue or analogue thereof comprising a nucleotide sequence substantially as set forth in SEQ ID NO:1 or SEQ ID NO:20 or a derivative thereof or capable of hybridising to SEQ ID NO:1 or SEQ ID NO:20 under low stringency conditions at 42°C and which encodes an amino acid sequence corresponding to an amino acid sequence set forth in SEQ ID NO:2 or SEQ ID NO:21 or a sequence having at least about 45% similarity to at least 10 contiguous amino acids in SEQ ID NO:2 or SEQ ID NO:21.

Still yet another aspect of the present invention contemplates a nucleic acid molecule comprising a sequence of nucleotides substantially as set forth in SEQ ID NO:1 or SEQ ID NO:20.

A further aspect of the present invention provides a novel cDNA or a derivative, homologue or analogue thereof in isolated form comprising a nucleotide sequence substantially as set forth in SEQ ID NO:1 or SEQ ID NO:20 or a nucleotide sequence having at least about 50% similarity to all or part thereof or a nucleotide sequence capable

of hybridising to the sequence set forth in SEQ ID NO:1 or SEQ ID NO:20 under low stringency conditions at 42°C.

Another further aspect of the present invention provides a nucleic acid molecule or derivative, homologue or analogue thereof comprising a nucleotide sequence encoding an amino acid sequence substantially as set forth in SEQ ID NO:5 or a derivative, homologue or mimetic thereof having at least about 45% or greater similarity to at least 30 contiguous amino acids in SEQ ID NO:5.

In another aspect there is provided a nucleic acid molecule or derivative, homologue or analogue thereof comprising a nucleotide sequence encoding an amino acid sequence substantially as set forth in SEQ ID NO:8 or a derivative, homologue or mimetic thereof having at least about 45% or greater similarity to at least 30 contiguous amino acids in SEQ ID NO:8.

In still another aspect there is provided a nucleic acid molecule or derivative, homologue or analogue thereof comprising a nucleotide sequence encoding an amino acid sequence substantially as set forth in SEQ ID NO:11or a derivative, homologue or mimetic thereof having at least about 45% or greater similarity to at least 30 contiguous amino acids in SEQ ID NO:11.

In yet another aspect, the present invention provides a novel nucleic acid molecule or a derivative, homologue or analogue thereof in isolated form comprising a nucleotide sequence substantially as set forth in SEQ ID NO:4 or a nucleotide sequence having at least about 50% similarity to all or part thereof or a nucleotide sequence capable of hybridising to the sequence set forth in SEQ ID NO:4 under low stringency conditions at 42°C.

In still yet another aspect, the present invention provides a novel nucleic acid molecule or a derivative, homologue or analogue thereof in isolated form comprising a nucleotide sequence substantially as set forth in SEQ ID NO:7 or a nucleotide sequence having at

least about 50% similarity to all or part thereof or a nucleotide sequence capable of hybridising to the sequence set forth in SEQ ID NO:7 under low stringency conditions at 42°C.

In still another aspect, the present invention provides a novel nucleic acid molecule or a derivative, homologue or analogue thereof in isolated form comprising a nucleotide sequence substantially as set forth in SEQ ID NO:10 or a nucleotide sequence having at least about 50% similarity to all or part thereof or a nucleotide sequence capable of hybridising to the sequence set forth in SEQ ID NO:10 under low stringency conditions at 42°C.

A further aspect of the present invention contemplates a nucleic acid molecule or derivative, homologue or analogue thereof comprising a nucleotide sequence substantially as set forth in SEQ ID NO:4 or a derivative thereof capable of hybridising to SEQ ID NO:4 under low stringency conditions at 42°C and which encodes an amino acid sequence corresponding to an amino acid sequence set forth in SEQ ID NO:5 or a sequence having at least about 45% similarity to at least 30 contiguous amino acids in SEQ ID NO:5.

In another further aspect the present invention contemplates a nucleic acid molecule or derivative, homologue or analogue thereof comprising a nucleotide sequence substantially as set forth in SEQ ID NO:7 or a derivative thereof capable of hybridising to SEQ ID NO:7 under low stringency conditions at 42°C and which encodes an amino acid sequence corresponding to an amino acid sequence set forth in SEQ ID NO:8 or a sequence having at least about 45% similarity to at least 30 contiguous amino acids in SEQ ID NO:8.

In still another further aspect the present invention contemplates a nucleic acid molecule or derivative, homologue or analogue thereof comprising a nucleotide sequence substantially as set forth in SEQ ID NO:10 or a derivative thereof capable of hybridising to SEQ ID NO:10 under low stringency conditions at 42°C and which encodes an amino acid sequence corresponding to an amino acid sequence set forth in SEQ ID NO:11 or a

sequence having at least about 45% similarity to at least 30 contiguous amino acids in SEQ ID NO:11.

Yet another further aspect of the present invention contemplates a nucleic acid molecule comprising a sequence of nucleotides substantially as set forth in SEQ ID NO:4, SEQ ID NO:7 or SEQ ID NO:10.

Still another further aspect of the present invention is directed to a isolated protein selected from the list consisting of:

(i) An isolated DEC-205 intergenic splice variant or a derivative, homologue, analogue, chemical equivalent or mimetic thereof.

(ii) An isolated DEC-205/DCL-1 intergenic splice variant or a derivative, homologue, analogue, chemical equivalent or mimetic thereof.

(iii) A protein having an amino acid sequence substantially as set forth in SEQ ID NO:2 or SEQ ID NO:21 or a derivative, homologue or mimetic thereof or a sequence having at least about 45% similarity to at least 30 contiguous amino acids in SEQ ID NO:2 or SEQ ID NO:21 or a derivative, homologue, analogue, chemical equivalent or mimetic of said protein.

(iv) A protein encoded by a nucleotide sequence substantially as set forth in SEQ ID NO:1 or SEQ ID NO:20 or a derivative, homologue or analogue of said nucleotide sequence or a derivative, homologue, analogue, chemical equivalent or mimetic of said protein.

(v) A protein encoded by a nucleotide sequence substantially as set forth in SEQ ID NO:1 or SEQ ID NO:20 or a derivative, homologue or analogue thereof or a sequence encoding an amino acid sequence having at least about 45% similarity to

at least 30 contiguous amino acids in SEQ ID NO:2 or SEQ ID NO:21 or a derivative, homologue, analogue, chemical equivalent or mimetic of said protein.

(vi) A protein encoded by a nucleic acid molecule capable of hybridising to the nucleotide sequence set forth in SEQ ID NO:1 or SEQ ID NO:20 or a derivative, homologue or analogue thereof under low stringency conditions at 42°C or a derivative, homologue, analogue, chemical equivalent or mimetic of said protein.

(vii) A protein encoded by a nucleic acid molecule capable of hybridising to the nucleotide sequence as set forth in SEQ ID NO:1 or SEQ ID NO:20 or a derivative, homologue or analogue thereof under low stringency conditions at 42°C and which encodes an amino acid sequence substantially as set forth in SEQ ID NO:2 or SEQ ID NO:21 or a derivative, homologue or mimetic thereof or an amino acid sequence having at least about 45% similarity to at least 30 contiguous amino acids in SEQ ID NO:2 or SEQ ID NO:21.

(viii) A protein having an amino acid sequence substantially as set forth in SEQ ID NO:5, SEQ ID NO:8, or SEQ ID NO:11 or a derivative, homologue or mimetic thereof or a sequence having at least about 45% similarity to at least 30 contiguous amino acids in SEQ ID NO:5, SEQ ID NO:8, or SEQ ID NO:11 or a derivative, homologue, analogue, chemical equivalent or mimetic of said protein.

(ix) A protein encoded by a nucleotide sequence substantially as set forth in SEQ ID NOs:4, 7 or 10 or a derivative, homologue or analogue of said nucleotide sequence or a derivative, homologue, analogue, chemical equivalent or mimetic of said protein.

(x) A protein encoded by a nucleotide sequence substantially as set forth in SEQ ID NOs:4, 7 of 10 or a derivative, homologue or analogue thereof or a sequence encoding an amino acid sequence having at least about 45% similarity to at least 30

contiguous amino acids in SEQ ID NOs:5, 8 or 11 or a derivative, homologue, analogue, chemical equivalent or mimetic of said protein.

(xi) A protein encoded by a nucleic acid molecule capable of hybridising to the nucleotide sequence set forth in SEQ ID NOs:4, 7 or 10 or a derivative, homologue or analogue thereof under low stringency conditions at 42°C or a derivative, homologue, analogue, chemical equivalent or mimetic of said protein

(xii) A protein encoded by a nucleic acid molecule capable of hybridising to the nucleotide sequence as set forth in SEQ ID NOs:4, 7 or 10 or a derivative, homologue or analogue thereof under low stringency conditions at 42°C and which encodes an amino acid sequence substantially as set forth in SEQ ID NOs:5, 8 or 11 or a derivative, homologue or mimetic thereof or an amino acid sequence having at least about 45% similarity to at least 30 contiguous amino acids in SEQ ID NOs:5, 8 or 11.

(xiii) A protein as defined in any one of paragraphs (i) to (xii) in a homodimeric form.

(xiv) A protein as defined in any one of paragraphs (i) to (xii) in a heterodimeric form.

Another aspect of the present invention contemplates a method of modulating *DEC-205 SV* expression or DEC-205 SV functional activity in a mammal, said method comprising administering to said mammal an agent for a time and under conditions sufficient to up-regulate, down-regulate or otherwise modulate expression of *DEC-205 SV* or functioning of DEC-205 SV.

Yet another aspect of the present invention is directed to a method for modulating *DCL-1* expression or DCL-1 functional activity in a mammal, said method comprising administering to said mammal an agent for a time and under conditions sufficient to up-regulate, down-regulate or otherwise modulate said expression or functioning.

Still another aspect of the present invention contemplates a method for regulating cellular activity in a subject said method comprising administering to said subject an effective amount of an agent for a time and under conditions sufficient to modulate *DEC-205 SV* expression of DEC-205 SV functional activity.

In yet another aspect there is contemplated a method of regulating cellular activity in a subject said method comprising administering to said subject an effective amount of an agent for a time and conditions sufficient to modulate *DCL-1* expression or DCL-1 functional activity.

In yet still another aspect there is provided a method for the treatment and/or prophylaxis of a condition characterised by aberrant, unwanted or otherwise inappropriate functioning of DEC-205 SV or DCL-1 in a subject, said method comprising administering to said subject an effective amount of an agent as hereinbefore defined for a time and under conditions sufficient to modulate the expression of *DEC-205 SV or DCL-1* and/or functioning of DEC-205 SV or DCL-1.

In still yet another aspect there is provided a method for the treatment of Hodgkin's lymphoma in a mammal, said method comprising administering to said mammal an effective amount of a cytolytic and/or cytotoxic agent which agent interacts or otherwise associates with DEC-205 SV, for a time and under conditions sufficient for said agent to lyse, apoptose or otherwise kill Hodgkin and Reed-Sternberg cells.

Single and three letter abbreviations used throughout the specification are defined in Table 1.

TABLE 1

Single and three letter amino acid abbreviations

Amino Acid	Three-letter Abbreviation	One-letter Symbol
Alanine	Ala	A
Arginine	Arg	R
Asparagine	Asn	N
Aspartic acid	Asp	D
Cysteine	Cys	C
Glutamine	Gln	Q
Glutamic acid	Glu	E
Glycine	Gly	G
Histidine	His	H
Isoleucine	Ile	I
Leucine	Leu	L
Lysine	Lys	K
Methionine	Met	M
Phenylalanine	Phe	F
Proline	Pro	P
Serine	Ser	S
Threonine	The	T
Tryptophan	Trp	W
Tyrosine	Tyr	Y
Valine	Val	V
Any residue	Xaa	X

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1. Identification of the cDNA clone encoding DEC-205/DCL-1 fusion. (A) A schematic presentation of DEC-205 mRNA (top, partial structure) and two representative clones (pB30-3 and pB30-1) isolated from the DEC-205 3'-RACE product. The boxes in the DEC-205 mRNA indicate domain structures, including CRDs, a TM and CP. Wide black bars indicate the DNA sequence for DEC-205[17] and wide shaded bars indicate the DNA sequence for the novel C-type lectin DCL-1 (KIAA0022).[22] The broken line indicates the position of the junction between DEC-205 and DCL-1. (B) The DNA and corresponding amino acids sequence adjacent to the junction for DEC-205/DCL-1 fusion protein. Sequence of the pB30-3 and pB30-1 were aligned with DEC-205 (top) and DCL-1 (bottom) sequences. An arrow indicates the DEC-205/DCL-1 junction, apparent after gene analysis was performed to assign the exon-intron junction of DEC-205 and DCL-1 gene. SP, signal peptide; CRD, carbohydrate recognition domain; TM, transmembrane domain; CP, cytoplasmic domain.

Figure 2. The DEC-205/DCL-1 fusion mRNA encodes the entire DEC-205 ectodomain. The L428 cDNA was subjected to RT-PCR using either DEC-205 specific reverse primer (085) or DCL-1 specific reverse primer (086) in combination with various DEC-205 specific forward primers (078, 088, 090, 092 and 094), and fractionated with 0.8% (w/v) agarose gel electrophoresis. The positions of these gene specific primers are indicated as arrows in the schematic diagram (bottom). The doublets obtained with several sets of primer combinations correspond to alternatively spliced DEC-205 mRNA (see text). SP, signal peptide; CR, cysteine-rich domain; FN, fibronectin type II domain; CRD, carbohydrate recognition domain; TM, transmembrane domain; CP, cytoplasmic domain.

Figure 3. ***The DEC-205/DCL-1 fusion mRNA is predominantly expressed by HRS cell lines.*** Total RNA from hematopoietic cell lines were subjected to Northern blot analysis, probed sequentially with the DCL-1 (top panel) and DEC-205 (middle panel). The bottom panel shows methylene blue staining of 28S ribosomal RNA.

Figure 4. The DEC-205 and DCL-1 gene are juxtaposed in chromosome band 2q24. A schematic drawing of DEC-205 (partial) and DCL-1 mRNA (top), DEC-205 (partial) and DCL-1 genes on chromosome 2q24 (middle) and DEC-205/DCL-1 fusion mRNA (bottom). In the top and bottom drawings, boxes indicate domain structures (please see keys in Figure 2). In the middle panel, boxes indicate exons.

Figure 5. DEC-205/DCL-1 fusion mRNA is translated to the fusion protein. (A) The cell lysates from HRS cell lines (L428, HDLM-2 and KM-H2), HEL and Jurkat cells were immunoprecipitated with anti DEC-205 CP, anti DCL-1 CP peptide antisera or non immune rabbit IgG, and the immune complexes were subjected to Western blot analysis using DEC-205 mAbs (M335 plus MMRI-7). The signals were detected by ECL on X-ray films. (B) The cell lysates as above were applied to a ELISA plate coated with DEC-205 mAbs, and bound DEC-205 or DEC-205/DCL-1 fusion protein was detected with anti DEC-205 CP (for DEC-205) or anti DCL-1 CP (for DCL-1). The signals were detected with OPD at 492 nm.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is predicated, in part, on the identification of novel DEC-205 splice variants. More particularly, the inventors have identified RNA splice variants of DEC-205 which encode an intact DEC-205 ectodomain in addition to a novel carbohydrate recognition domain, transmembrane domain and cytoplasmic domain. Still further, the inventors have determined that the generation of these novel splice variants is likely the result of an intergenic splicing event which leads to the formation of a fusion mRNA comprising both partial DEC-205 mRNA and a novel carbohydrate recognition domain, transmembrane domain and cytoplasmic domain encoding mRNA sequence. In investigating these unique cistronic mRNAs, the inventors have yet further determined that the novel carbohydrate recognition domain, transmembrane and cytoplasmic domains, which are spliced together with a partial DEC-205 mRNA transcript in order to form the subject novel DEC-205 splice variants, corresponds to a novel type I C-type lectin, herein termed "DCL-1". The identification of these novel molecules now permits the identification and rational design of a range of products for use in prophylaxis, therapy, diagnosis and antibody generation including, for example, in the context of diagnosing and/or treating disease conditions characterised by the presence of Reed-Sternberg cells.

Accordingly, one aspect of the present invention provides a novel nucleic acid molecule in isolated form wherein said nucleic acid molecule comprises a novel DEC-205 intergenic splice variant.

Reference to "DEC-205 intergenic splice variant" should be understood as a reference to an RNA product of a splicing event which results in the introduction of non-DEC-205 nucleic acid material to DEC-205 nucleic acid material. This may occur at the level of either the primary RNA transcript or the mRNA. Preferably, the DEC-205 intergenic splice variant is an mRNA DEC-205 intergenic splice variant. In this regard, it should be understood that the subject splice variant may be a splice variant of any form of DEC-205 such as any allelic form of DEC-205. Still further it should be understood that the DEC-205 encoding portion of the splice variants of the present invention may not necessarily

correspond to the entire DEC-205 encoding mRNA. For example, the variants exemplified herein encode a molecule comprising the DEC-205 ectodomain (being the signal peptide, cysteine rich domain, fibronectin type II domain and carbohydrate recognition domains 1-10) followed by the DCL-1 carbohydrate recognition domain, transmembrane domain and cytoplasmic domain. In a most preferred embodiment, the subject non-DEC-205 nucleic acid material corresponds to all or part of the DCL-1 gene or its transcribed RNA product. The fusion/splicing together of all or part of DEC-205 nucleic acid material with DCL-1 nucleic acid material to form a novel DEC-205 intergenic splice variant is herein referred to as a "DEC-205/DCL-1 intergenic splice variant".

According to this preferred embodiment there is provided a novel nucleic acid molecule in isolated form wherein said nucleic acid molecule comprises a DEC-205/DCL-1 intergenic splice variant.

Reference to "DEC-205" should be understood as a reference to a molecule of the family of type I transmembrane C-type lectin receptors that are, *inter alia*, expressed by dendritic cells. Reference to "DCL-1" is hereinafter defined.

The present invention still more particularly provides a nucleic acid molecule or derivative, homologue or analogue thereof comprising a nucleotide sequence encoding an amino acid sequence substantially as set forth in SEQ ID NO:2 or SEQ ID NO:21 or a derivative, homologue or mimetic thereof having at least about 45% or greater similarity to at least 30 contiguous amino acids in SEQ ID NO:2 or SEQ ID NO:21.

The term "similarity" as used herein includes exact identity between compared sequences at the nucleotide or amino acid levels. Where there is non-identity at the nucleotide level "similarity" includes differences between sequences which result in different amino acids that are nevertheless related to each other at the structural, functional, biochemical and/or conformational levels. Where there is non-identity at the amino acid level, "similarity" includes amino acids that are nevertheless related to each other at the structural, functional, biochemical and/or conformational levels. The percentage similarity may be greater than

45% such as at least 50% or at least 55% or at least 60% or at least 65% or at least 70% or at least 75% or at least 80% or at least 85% or at least 90% or at least 95% or higher. To determine the percent identity of two amino acid sequences or of two nucleic acids, the sequences may be aligned for optimal comparison purposes (e.g., gaps can be introduced in the sequence of a first amino acid or nucleic acid sequence for optimal alignment with a second amino or nucleic acid sequence). The amino acid residues or nucleotides at corresponding amino acid positions or nucleotide positions can then be compared. When a position in the first sequence is occupied by the same amino acid residue or nucleotide as the corresponding position in the second sequence, then the molecules are identical at that position. The percent identity between the two sequences is a function of the number of identical positions shared by the sequences (i.e. % identity = # of identical positions/total # of overlapping positions x 100). Preferably, the two sequences are the same length. The determination of percent identity or homology between two sequences can be accomplished using a mathematical algorithm. A suitable, mathematical algorithm utilized for the comparison of two sequences is the algorithm of Karlin and Altschul (1990) *Proc. Natl. Acad. Sci. USA 87:*2264-2268, modified as in Karlin and Altschul (1993) *Proc. Natl. Acad. Sci. USA 90:*5873-5877. Such an algorithm is incorporated into the NBLAST and XBLAST programs of Altschul, *et al.* (1990) *J. Mol. Biol. 215:*403-410. BLAST nucleotide searches can be performed with the NBLAST program, score = 100, wordlength = 12 to obtain nucleotide sequences homologous to the nucleic acid molecules of the invention. BLAST protein searches can be performed with XBLAST program, score = 50, wordlength = 3 to obtain amino acid sequences homologous to the protein molecules of the invention. To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul *et al.* (1997) *Nucleic Acids Res. 25:*3389-3402. When utilizing BLAST and Gapped BLAST programs, the default parameters of the respective programs (e.g., XBLAST and NBLAST) can be used. See http://www.ncbi.nlm.nih.gov. Another example of a mathematical algorithm utilized for the comparison of sequences is the algorithm of Myers and Miller, CABIOS (1989). Such an algorithm is incorporated into the ALIGN program (version 2.0) which is part of the GCG sequence alignment software package. When utilizing the ALIGN program for comparing amino acid sequences, a PAM120 weight residue table, a gap length penalty of 12, and a gap penalty

of 4 can be used. The percent identity between two sequences can be determined using techniques similar to those described above, with or without allowing gaps. In calculating percent identity, only exact matches are counted. Yet another example of a suitable algorithm is one such Gap which considers all possible alignment and gap positions and creates an alignment with the largest number of matches bases and the fewest gaps. Gap uses the alignment method of Needleman and Wunsch. Gap reads a scoring matrix that contains values for ever possible GCG symbol match. GAP is available on ANGIS (Australian National Genomic Information Service) at website http://mel1.angis.org.au.

In another embodiment, the present invention provides a novel nucleic acid molecule or a derivative, homologue or analogue thereof in isolated form comprising a nucleotide sequence substantially as set forth in SEQ ID NO:1 or SEQ ID NO:20 or a nucleotide sequence having at least about 50% similarity to all or part thereof or a nucleotide sequence capable of hybridising to the sequence set forth in SEQ ID NO:1 or SEQ ID NO:20 under low stringency conditions at 42°C.

Preferably, the present invention contemplates a nucleic acid molecule or derivative, homologue or analogue thereof comprising a nucleotide sequence substantially as set forth in SEQ ID NO:1 or SEQ ID NO:20 or a derivative thereof or capable of hybridising to SEQ ID NO:1 or SEQ ID NO:20 under low stringency conditions at 42°C and which encodes an amino acid sequence corresponding to an amino acid sequence set forth in SEQ ID NO:2 or SEQ ID NO:21 or a sequence having at least about 45% similarity to at least 10 contiguous amino acids in SEQ ID NO:2 or SEQ ID NO:21.

More particularly, the present invention contemplates a nucleic acid molecule comprising a sequence of nucleotides substantially as set forth in SEQ ID NO:1 or SEQ ID NO:20.

Reference herein to a low stringency includes and encompasses from at least about 0% v/v to at least about 15% v/v formamide and from at least about 1M to at least about 2M salt for hybridisation, and at least about 1M to at least about 2M salt for washing conditions. Alternative stringency conditions may be applied where necessary, such as medium

stringency, which includes and encompasses from at least about 16% v/v to at least about 30% v/v formamide and from at least about 0.5M to at least about 0.9M salt for hybridisation, and at least about 0.5M to at least about 0.9M salt for washing conditions, or high stringency, which includes and encompasses from at least about 31% v/v to at least about 50% v/v formamide and from at least about 0.01M to at least about 0.15M salt for hybridisation, and at least about 0.01M to at least about 0.15M salt for washing conditions. Stringency may be measured using a range of temperature such as from about 40°C to about 65°C. Particularly useful stringency conditions are at 42°C. In general, washing is carried out at $T_m = 69.3 + 0.41\ (G + C)\ \% = -12°C$. However, the T_m of a duplex DNA decreases by 1°C with every increase of 1% in the number of mismatched based pairs (Bonner *et al* (1973) *J. Mol. Biol.*, **81**:123).

The nucleic acid molecule according to this aspect of the present invention corresponds herein to "*DEC-205 SV*". Reference to the expression product appears in non-italicised text. Without limiting the present invention to any one theory or mode of action, it has been determined that *DEC-205 SV* mRNA encodes the full ectodomain of DEC-205 together with the carbohydrate recognition domain, transmembrane and cytoplasmic domain of DCL-1. The ectodomain of DEC-205 comprises a signal peptide, cysteine rich domain, fibronectin type II domain and 10 lectin-like carbohydrate recognition domains. The junction of DEC-205/DCL-1 mRNA is in frame, indicating that *DEC-205 SV* mRNA can be translated successfully. Both the DEC-205 and DCL-1 genes map to chromosome 2q24 and consist of 35 and 6 exons, respectively. These genes are separated by 5.4 kb. As detailed hereinbefore, the DCL-1 gene is a novel gene which has been identified by the inventors in respect of the present invention. More detailed discussion in relation to DCL-1 is provided hereinafter.

In one embodiment a *DEC-205 SV* mRNA is thought to be generated by transcribing a cistronic mRNA containing DEC-205 and DCL-1 gene followed by splicing out of DEC-205 exon 35 and DCL exon 1 (herein referred to as the "DEC-205 SV34"). In another embodiment, another *DEC-205 SV* mRNA is generated by transcribing a cistronic mRNA containing DEC-205 and DCL-1 gene followed by splicing out of DEC-205 exons 34 and

35, together with DCL-1 exon 1. Accordingly, there occurs fusion of the DEC-205 exon 33 to DCL-1 exon 2 (herein referred to as the "DEC-205 SV33"). The generation of DEC-205 SV therefore involves an intergenic splicing event, being an extremely rare event. The inventors have determined that the 5' proximal promoter regions for DEC-205 and DCL-1 show independent promoter activity, thereby confirming their status as independent genes. This further confirms that the generation of DEC-205 SV clearly involves an intergenic splicing event.

The human DEC-205 SV34 expression product is defined by the amino acid sequence set forth in SEQ ID NO:2 while the DEC-205 SV33 expression product is defined by the amino acid sequence set forth in SEQ ID NO:21. The cDNA nucleotide sequence for human DEC-205 SV34 is set forth in SEQ ID NO:1 and the cDNA nucleotide sequence for human DEC-205 SV33 is set forth in SEQ ID NO:20. The nucleic acid molecules encoding the DEC-205 SV expression products are preferably a sequence of deoxyribonucleic acids such as a cDNA sequence or a genomic sequence. A cDNA sequence may optionally comprise all or some of the 5' or 3' untranslated regions while a genomic sequence may also comprise introns. A genomic sequence may also include a promoter region or other regulatory regions. It should also be understood that the subject nucleic acid molecule may be a sequence of ribonucleic acids such as mRNA.

In a particularly preferred embodiment, the present invention provides a novel cDNA or a derivative, homologue or analogue thereof in isolated form comprising a nucleotide sequence substantially as set forth in SEQ ID NO:1 or SEQ ID NO:20 or a nucleotide sequence having at least about 50% similarity to all or part thereof or a nucleotide sequence capable of hybridising to the sequence set forth in SEQ ID NO:1 or SEQ ID NO:20 under low stringency conditions at 42°C.

As detailed hereinbefore, the present invention extends to nucleic acid molecules complementary to *DEC-205 SV*. In this regard, two examples of such complementary nucleic acid molecules are the nucleic acid molecules provided in SEQ ID NO:3 and SEQ ID NO:22 which are complementary to SEQ ID NO:1 and SEQ ID NO:20, respectively.

In a related aspect, the inventors have determined that the DCL-1 gene with which the DEC-205 is intergenically spliced to create the novel splice variants of the present invention is, itself, a novel gene. Specifically, it has been determined that DCL-1 corresponds to a unique type I transmembrane C-type lectin, the ectodomain of which contains only one CRD, whereas other type I transmembrane C-type lectins contain more than one domain. The DCL-1 expression product contains several putative motifs including a Tyr-based internalisation, a cluster of acidic amino acids and Ser- and Tyr-phosphorylation motifs. Without limiting the present invention to any one theory or mode of action, these features suggest that DCL-1 mediates not only endocytosis and late endosome targeting but also signalling.

Accordingly, another aspect of the present invention provides a nucleic acid molecule or derivative, homologue or analogue thereof comprising a nucleotide sequence encoding an amino acid sequence substantially as set forth in SEQ ID NO:5 or a derivative, homologue or mimetic thereof having at least about 45% or greater similarity to at least 30 contiguous amino acids in SEQ ID NO:5.

In another aspect there is provided a nucleic acid molecule or derivative, homologue or analogue thereof comprising a nucleotide sequence encoding an amino acid sequence substantially as set forth in SEQ ID NO:8 or a derivative, homologue or mimetic thereof having at least about 45% or greater similarity to at least 30 contiguous amino acids in SEQ ID NO:8.

In still another aspect there is provided a nucleic acid molecule or derivative, homologue or analogue thereof comprising a nucleotide sequence encoding an amino acid sequence substantially as set forth in SEQ ID NO:11 or a derivative, homologue or mimetic thereof having at least about 45% or greater similarity to at least 30 contiguous amino acids in SEQ ID NO:11.

Reference to "similarity" should have the same meaning as hereinbefore provided.

In another embodiment, the present invention provides a novel nucleic acid molecule or a derivative, homologue or analogue thereof in isolated form comprising a nucleotide sequence substantially as set forth in SEQ ID NO:4 or a nucleotide sequence having at least about 50% similarity to all or part thereof or a nucleotide sequence capable of hybridising to the sequence set forth in SEQ ID NO:4 under low stringency conditions at 42°C.

In yet another embodiment, the present invention provides a novel nucleic acid molecule or a derivative, homologue or analogue thereof in isolated form comprising a nucleotide sequence substantially as set forth in SEQ ID NO:7 or a nucleotide sequence having at least about 50% similarity to all or part thereof or a nucleotide sequence capable of hybridising to the sequence set forth in SEQ ID NO:7 under low stringency conditions at 42°C.

In still another embodiment, the present invention provides a novel nucleic acid molecule or a derivative, homologue or analogue thereof in isolated form comprising a nucleotide sequence substantially as set forth in SEQ ID NO:10 or a nucleotide sequence having at least about 50% similarity to all or part thereof or a nucleotide sequence capable of hybridising to the sequence set forth in SEQ ID NO:10 under low stringency conditions at 42°C.

Preferably, the present invention contemplates a nucleic acid molecule or derivative, homologue or analogue thereof comprising a nucleotide sequence substantially as set forth in SEQ ID NO:4 or a derivative thereof capable of hybridising to SEQ ID NO:4 under low stringency conditions at 42°C and which encodes an amino acid sequence corresponding to an amino acid sequence set forth in SEQ ID NO:5 or a sequence having at least about 45% similarity to at least 30 contiguous amino acids in SEQ ID NO:5.

In another preferred embodiment, the present invention contemplates a nucleic acid molecule or derivative, homologue or analogue thereof comprising a nucleotide sequence

substantially as set forth in SEQ ID NO:7 or a derivative thereof capable of hybridising to SEQ ID NO:7 under low stringency conditions at 42°C and which encodes an amino acid sequence corresponding to an amino acid sequence set forth in SEQ ID NO:8 or a sequence having at least about 45% similarity to at least 30 contiguous amino acids in SEQ ID NO:8.

In still another preferred embodiment, the present invention contemplates a nucleic acid molecule or derivative, homologue or analogue thereof comprising a nucleotide sequence substantially as set forth in SEQ ID NO:10 or a derivative thereof capable of hybridising to SEQ ID NO:10 under low stringency conditions at 42°C and which encodes an amino acid sequence corresponding to an amino acid sequence set forth in SEQ ID NO:11 or a sequence having at least about 45% similarity to at least 30 contiguous amino acids in SEQ ID NO:11.

Most particularly, the present invention contemplates a nucleic acid molecule comprising a sequence of nucleotides substantially as set forth in SEQ ID NO:4, SEQ ID NO:7 or SEQ ID NO:10.

Reference to "stringency" should have the same meaning as hereinbefore provided.

The nucleic acid molecule according to this aspect of the present invention corresponds herein to "*DCL-1*". This gene has been determined in accordance with the present invention to encode a novel type I transmembrane C-type lectin which encodes only one CRD. The product of the DCL-1 gene is referred to herein as "DCL-1" (non-italicised text). DCL-1 is a protein for which intergenic splice variants exist, thereby resulting in the expression of a variety of intergenic isoforms. These have been hereinbefore described and are encompassed by the scope of the present invention. Further, a number of homologues of DCL-1 have been identified and described herein. Human DCL-1 is defined by the amino acid sequence set forth in SEQ ID NO:5, murine DCL-1 is defined by the amino acid sequence set forth in SEQ ID NO:8 and rat DCL-1 is defined by the amino acid sequence set forth in SEQ ID NO:11. The cDNA nucleotide sequences for

human DCL-1 are defined by the nucleotide sequence set forth in SEQ ID NO:4. Murine and rat cDNA DCL-1 sequences are defined by the nucleotide sequences set forth in SEQ ID NO:7 and 10, respectively. SEQ ID NO:13 discloses a partial sequence of bovine DCL-1. As detailed hereinbefore, the nucleic acid molecules encoding DCL-1 expression products are preferably a sequence of deoxyribonucleic acids such as cDNA sequences or a genomic sequence. A cDNA sequence may optionally comprise all or some of the 5' or 3' untranslated regions while a genomic sequence may also comprise introns. A genomic sequence may also include a promoter region or other regulatory regions. It should also be understood that the subject nucleic acid molecules may be a sequence of ribonucleic acids such as mRNA.

The present invention extends to nucleic acid molecules complementary to DCL-1. In this regard, examples of such complementary nucleic acid molecules are the nucleic acid molecules provided in SEQ ID NOs:6, 9 and 12 which are complementary to SEQ ID NOs:4, 7 and 10, respectively.

The nucleic acid molecule of the present invention is preferably in isolated form or ligated to a vector, such as an expression vector. By "isolated" is meant a nucleic acid molecule having undergone at least one purification step and this is conveniently defined, for example, by a composition comprising at least about 10% subject nucleic acid molecule, preferably at least about 20%, more preferably at least about 30%, still more preferably at least about 40-50%, even still more preferably at least about 60-70%, yet even still more preferably 80-90% or greater of subject nucleic acid molecule relative to other components as determined by molecular weight, encoding activity, nucleotide sequence, base composition or other convenient means. The nucleic acid molecule of the present invention may also be considered, in a preferred embodiment, to be biologically pure.

The nucleic acid molecule may be ligated to an expression vector capable of expression in a prokaryotic cell (e.g. *E.coli*) or a eukaryotic cell (e.g. yeast cells, fungal cells, insect cells, mammalian cells or plant cells). The nucleic acid molecule may be ligated or fused or otherwise associated with a nucleic acid molecule encoding another entity such as, for

example, a signal peptide. It may also comprise additional nucleotide sequence information fused, linked or otherwise associated with it either at the 3' or 5' terminal portions or at both the 3' and 5' terminal portions. The nucleic acid molecule may also be part of a vector, such as an expression vector. The latter embodiment facilitates production of recombinant forms of DEC-205 SV or DCL-1 which forms are encompassed by the present invention.

The expression product of the splice variant disclosed herein is a novel DEC-205 intergenic splice variant having an amino acid sequence set forth in SEQ ID NO:2 or SEQ ID NO:21 or is a derivative, homologue, analogue, chemical equivalent or mimetic thereof or is a molecule having an amino acid sequence of at least about 45% similarity to at least 30 contiguous amino acids in the amino acid sequence as set forth in SEQ ID NO:2 or SEQ ID NO:21 or a derivative, homologue, analogue, chemical equivalent or mimetic thereof.

The expression product of the novel lectin molecule disclosed herein is a novel DCL-1 molecule having an amino acid sequence set forth in SEQ ID NOs:5, 8 or 11 or is a derivative, homologue, analogue, chemical equivalent or mimetic thereof or is a molecule having an amino acid sequence of at least about 45% similarity to at least 30 contiguous amino acids in the amino acid sequence set forth in SEQ ID NO:5, 8 or 11, respectively or a derivative, homologue, analogue, chemical equivalent or mimetic thereof.

Accordingly, another aspect of the present invention is directed to a isolated protein selected from the list consisting of:

(ii) An isolated DEC-205 intergenic splice variant or a derivative, homologue, analogue, chemical equivalent or mimetic thereof.

(ii) An isolated DEC-205/DCL-1 intergenic splice variant or a derivative, homologue, analogue, chemical equivalent or mimetic thereof.

(xv) A protein having an amino acid sequence substantially as set forth in SEQ ID NO:2 or SEQ ID NO:21 or a derivative, homologue or mimetic thereof or a sequence having at least about 45% similarity to at least 30 contiguous amino acids in SEQ ID NO:2 or SEQ ID NO:21 or a derivative, homologue, analogue, chemical equivalent or mimetic of said protein.

(xvi) A protein encoded by a nucleotide sequence substantially as set forth in SEQ ID NO:1 or SEQ ID NO:20 or a derivative, homologue or analogue of said nucleotide sequence or a derivative, homologue, analogue, chemical equivalent or mimetic of said protein.

(xvii) A protein encoded by a nucleotide sequence substantially as set forth in SEQ ID NO:1 or SEQ ID NO:20 or a derivative, homologue or analogue thereof or a sequence encoding an amino acid sequence having at least about 45% similarity to at least 30 contiguous amino acids in SEQ ID NO:2 or SEQ ID NO:21 or a derivative, homologue, analogue, chemical equivalent or mimetic of said protein.

(xviii) A protein encoded by a nucleic acid molecule capable of hybridising to the nucleotide sequence set forth in SEQ ID NO:1 or SEQ ID NO:20 or a derivative, homologue or analogue thereof under low stringency conditions at 42°C or a derivative, homologue, analogue, chemical equivalent or mimetic of said protein.

(xix) A protein encoded by a nucleic acid molecule capable of hybridising to the nucleotide sequence as set forth in SEQ ID NO:1 or SEQ ID NO:20 or a derivative, homologue or analogue thereof under low stringency conditions at 42°C and which encodes an amino acid sequence substantially as set forth in SEQ ID NO:2 or SEQ ID NO:21 or a derivative, homologue or mimetic thereof or an amino acid sequence having at least about 45% similarity to at least 30 contiguous amino acids in SEQ ID NO:2 or SEQ ID NO:21.

(xx) A protein having an amino acid sequence substantially as set forth in SEQ ID NO:5, SEQ ID NO:8, or SEQ ID NO:11 or a derivative, homologue or mimetic thereof or a sequence having at least about 45% similarity to at least 30 contiguous amino acids in SEQ ID NO:5, SEQ ID NO:8, or SEQ ID NO:11 or a derivative, homologue, analogue, chemical equivalent or mimetic of said protein.

(xxi) A protein encoded by a nucleotide sequence substantially as set forth in SEQ ID NOs:4, 7 or 10 or a derivative, homologue or analogue of said nucleotide sequence or a derivative, homologue, analogue, chemical equivalent or mimetic of said protein.

(xxii) A protein encoded by a nucleotide sequence substantially as set forth in SEQ ID NOs:4, 7 of 10 or a derivative, homologue or analogue thereof or a sequence encoding an amino acid sequence having at least about 45% similarity to at least 30 contiguous amino acids in SEQ ID NOs:5, 8 or 11 or a derivative, homologue, analogue, chemical equivalent or mimetic of said protein.

(xxiii) A protein encoded by a nucleic acid molecule capable of hybridising to the nucleotide sequence set forth in SEQ ID NOs:4, 7 or 10 or a derivative, homologue or analogue thereof under low stringency conditions at 42°C or a derivative, homologue, analogue, chemical equivalent or mimetic of said protein

(xxiv) A protein encoded by a nucleic acid molecule capable of hybridising to the nucleotide sequence as set forth in SEQ ID NOs:4, 7 or 10 or a derivative, homologue or analogue thereof under low stringency conditions at 42°C and which encodes an amino acid sequence substantially as set forth in SEQ ID NOs:5, 8 or 11 or a derivative, homologue or mimetic thereof or an amino acid sequence having at least about 45% similarity to at least 30 contiguous amino acids in SEQ ID NOs:5, 8 or 11.

(xxv) A protein as defined in any one of paragraphs (i) to (xii) in a homodimeric form.

(xxvi) A protein as defined in any one of paragraphs (i) to (xii) in a heterodimeric form.

The term "protein" should be understood to encompass peptides, polypeptides and proteins. The protein may be glycosylated or unglycosylated and/or may contain a range of other molecules fused, linked, bound or otherwise associated to the protein such as amino acids, lipids, carbohydrates or other peptides, polypeptides or proteins. Reference hereinafter to a "protein" includes a protein comprising a sequence of amino acids as well as a protein associated with other molecules such as amino acids, lipids, carbohydrates or other peptides, polypeptides or proteins.

The protein of the present invention is preferably in isolated form. By "isolated" is meant a protein having undergone at least one purification step and this is conveniently defined, for example, by a composition comprising at least about 10% subject protein, preferably at least about 20%, more preferably at least about 30%, still more preferably at least about 40-50%, even still more preferably at least about 60-70%, yet even still more preferably 80-90% or greater of subject protein relative to other components as determined by molecular weight, amino acid sequence or other convenient means. The protein of the present invention may also be considered, in a preferred embodiment, to be biologically pure.

The DEC-205 SV or DCL-1 of the present invention may be in multimeric form meaning that two or more molecules are associated together. Where the same DEC-205 SV or DCL-1 molecules are associated together, the complex is a homomultimer. An example of a homomultimer is a homodimer. Where at least one DEC-205 SV or DCL-1 is associated with at least one non-DEC-205 SV or DCL-1 molecule, then the complex is a heteromultimer such as a heterodimer.

The ability to produce recombinant DEC-205 SV or DCL-1 permits the large scale production of these molecules for commercial use. The DEC-205 SV or DCL-1 may need to be produced as part of a large peptide, polypeptide or protein which may be used as is or

may first need to be processed in order to remove the extraneous proteinaceous sequences. Such processing includes digestion with proteases, peptidases and amidases or a range of chemical, electrochemical, sonic or mechanical disruption techniques.

Notwithstanding that the present invention encompasses recombinant proteins, chemical synthetic techniques are also preferred in synthesis of DEC-205 SV or DCL-1.

DEC-205 SV or DCL-1 according to the present invention is conveniently synthesised based on molecules isolated from a mammal. Isolation of these molecules may be accomplished by any suitable means such as by chromotographic separation, for example using CM-cellulose ion exchange chromotography followed by Sephadex (e.g. G-50 column) filtration. Many other techniques are available including HPLC, PAGE amongst others.

DEC-205 SV or DCL-1 may be synthesised by solid phase synthesis using F-moc chemistry as described by Carpino *et al.* (1991). DEC-205 SV and fragments thereof may also be synthesised by alternative chemistries including, but not limited to, t-Boc chemistry as described in Stewart *et al.* (1985) or by classical methods of liquid phase peptide synthesis.

The protein and/or gene is preferably from a human, primate, livestock animal (e.g. sheep, pig, cow, horse, donkey), laboratory test animal (e.g. mouse, rabbit, rat, guinea pig), companion animal (e.g. dog, cat), captive wild animal (e.g. fox, kangaroo, deer), aves (e.g. chicken, geese, duck, emu, ostrich), reptile or fish. Most preferably, the gene is of human or primate origin.

Without limiting the present invention to any one theory or mode of action, genes encoding DEC-205 and DCL-1 are juxtaposed within chromosome band 2q24 and are separated by only approximately 5.4kb. These two genes are independent genes because both DEC-205 and DLC-1 mRNA are expressed independently in haematopoietic cell lines. Further, luciferase reporter assay studies show that both the 5'- proximal promoters of DEC-205

and DCL-1 have independent promoter activities. Still without limiting the invention in any way, all Hodgkin and Reed-Sternberg cells express the 9.5kb DEC-205 SV mRNA indicating that expression of this mRNA is highly regulated. Accordingly, it is thought that mechanisms which transcriptionally control expression of this splice variant molecule may be involved in the pathogenesis of Hodgkin's disease. Still further, the presence of this molecule in classical Hodgkin's lymphoma provides a target for antibody or T-cell mediated immunotherapy for this disease condition.

The present invention therefore contemplates a method of modulating *DEC-205 SV* expression or DEC-205 SV functional activity in a mammal, said method comprising administering to said mammal an agent for a time and under conditions sufficient to up-regulate, down-regulate or otherwise modulate expression of *DEC-205 SV* or functioning of DEC-205 SV.

For example, *DEC-205 SV* antisense sequences such as oligonucleotides may be introduced into a cell to down-regulate the expression of *DEC-205/DCL-1*. Conversely, a nucleic acid molecule encoding DEC-205/DCL-1 or a derivative thereof may be introduced to enhance the functioning of DEC-205 SV in any cell expressing the endogenous *DEC-205 SV* gene. Although the preferred method is to down-regulate the expression of this molecule as a means for therapeutically or prophylactically treating Hodgkin's lymphoma, it should be understood that the present invention also extends to up-regulation of the expression of this molecule which may be desired in certain circumstances, such as for the purpose of creating cell lines for further studies.

Reference to "*DEC-205 SV*" should be understood as a reference to all splice variant forms of this molecule including, for example, the *DEC-205 SV34* and *DEC-205 SV33* forms of this splice variant.

In accordance with the other aspect of the present invention, and without limiting this aspect of the present invention in any way, as detailed hereinbefore DCL-1 is a unique type I transmembrane C-type lectin which expresses an ectodomain containing only one CRD.

Most other type I transmembrane C-type lectins contain more than one domain. It is thought that since DCL-1 comprises putative motifs including a Tyr based internalisation, a cluster of acidic amino acids and Ser- and Tyr-phosphorylation motifs, that DCL-1 mediates not only endocytosis and late endosome targeting but also signalling. Further, it has been found that this molecule is expressed in myeloid and B cells.

Accordingly, another aspect of the present invention is directed to a method for modulating *DCL-1* expression or DCL-1 functional activity in a mammal, said method comprising administering to said mammal an agent for a time and under conditions sufficient to up-regulate, down-regulate or otherwise modulate said expression or functioning.

The cloning and sequencing of these molecules and their expression products now provides a mechanism for both the development of diagnosis/prognosis methodology and the prophylactic and therapeutic treatment of conditions such as Hodgkin's lymphoma. Accordingly, the present invention contemplates therapeutic, prophylactic, diagnostic and prognostic uses of DEC-205 SV amino acid and nucleic acid molecules, DCL-1 amino acid and nucleic acid molecules and agonistic and antagonistic agents thereto, for the regulation of cell functional activity.

The present invention contemplates, therefore, a method for regulating cellular activity in a subject said method comprising administering to said subject an effective amount of an agent for a time and under conditions sufficient to modulate *DEC-205 SV* expression of DEC-205 SV functional activity.

In yet another aspect there is contemplated a method of regulating cellular activity in a subject said method comprising administering to said subject an effective amount of an agent for a time and conditions sufficient to modulate *DCL-1* expression or DCL-1 functional activity.

Reference to "cellular activity" should be understood as a reference to one or more of the functional activities which are directly or indirectly regulated via the DEC-205 SV or

DCL-1 expression products. This includes, but is not limited to, cellular endocytosis, late endosome targeting, signalling (in respect of the DCL-1 molecule) and Hodgkin and Reed-Sternberg cell functioning (in respect of the DEC-205 SV molecule).

In terms of achieving the up or down-regulation of DEC-205 SV or DCL-1 expression or functioning, means for achieving this objective would be well known to the person of skill in the art and include, but are not limited to:

(i) Introducing into a cell a nucleic acid molecule encoding DEC-205 SV or DCL-1 or functional equivalent, derivative or analogue thereof in order to up-regulate the capacity of said cell to express DEC-205 SV or DCL-1, respectively.

(ii) Introducing into a cell a proteinaceous or non-proteinaceous molecule which modulates transcriptional and/or translational regulation of a gene, wherein this gene may be *DEC-205 SV or DCL-1* or functional portion thereof or some other gene which directly or indirectly modulates the expression of *DEC-205 SV or DCL-1.*

(iii) Introducing a proteinaceous or non-proteinaceous molecule which functions as an antagonist to the DEC-205 SV or DCL-1 expression product.

(iv) Introducing a proteinaceous or non-proteinaceous molecule which functions as an agonist of the DEC-205 SV or DCL-1 expression product.

The proteinaceous molecules described above may be derived from any suitable source such as natural, recombinant or synthetic sources and includes fusion proteins or molecules which have been identified following, for example, natural product screening. The reference to non-proteinaceous molecules may be, for example, a reference to a nucleic acid molecule or it may be a molecule derived from natural sources, such as for example natural product screening, or may be a chemically synthesised molecule. The present invention contemplates analogues of the DEC-205 SV or DCL-1 expression product or

small molecules capable of acting as agonists or antagonists. Chemical agonists may not necessarily be derived from the DEC-205 SV or DCL-1 expression product but may share certain conformational similarities. Alternatively, chemical agonists may be specifically designed to meet certain physiochemical properties. Antagonists may be any compound capable of blocking, inhibiting or otherwise preventing DEC-205 SV or DCL-1 from carrying out its normal biological function. Antagonists include monoclonal antibodies and antisense nucleic acids which prevent transcription or translation of *DEC-205 SV* or DCL-1 genes or mRNA in mammalian cells. Modulation of expression may also be achieved utilising antigens, RNA, ribosomes, DNAzymes, RNA aptamers, antibodies or molecules suitable for use in cosuppression. The proteinaceous and non-proteinaceous molecules referred to in points (i)-(iv), above, are herein collectively referred to as "modulatory agents".

Screening for the modulatory agents hereinbefore defined can be achieved by any one of several suitable methods including, but in no way limited to, contacting a cell comprising the *DEC-205 SV or DCL-1* gene or functional equivalent or derivative thereof with an agent and screening for the modulation of DEC-205 SV or DCL-1 protein production or functional activity, modulation of the expression of a nucleic acid molecule encoding DEC-205 SV or DCL-1 or modulation of the activity or expression of a downstream functional activity. Detecting such modulation can be achieved utilising techniques such as Western blotting, electrophoretic mobility shift assays and/or the readout of reporter genes

It should be understood that the *DEC-205 SV or DCL-1* gene or functional equivalent or derivative thereof may be naturally occurring in the cell which is the subject of testing or it may have been transfected into a host cell for the purpose of testing. Further, the naturally occurring or transfected gene may be constitutively expressed - thereby providing a model useful for, inter alia, screening for agents which down regulate DEC-205 SV or DCL-1 activity, at either the nucleic acid or expression product levels, or the gene may require activation - thereby providing a model useful for, inter alia, screening for agents which up regulate *DEC-205 SV or DCL-1* expression. Further, to the extent that a *DEC-205 SV or*

DCL-1 nucleic acid molecule is transfected into a cell, that molecule may comprise the entire *DEC-205 SV or DCL-1* gene or it may merely comprise a portion of the gene such as the portion which regulates expression of the DEC-205 SV or DCL-1 product. For example, the *DEC-205 SV or DCL-1* promoter region may be transfected into the cell which is the subject of testing. In this regard, where only the promoter is utilised, detecting modulation of the activity of the promoter can be achieved, for example, by ligating the promoter to a reporter gene. For example, the promoter may be ligated to luciferase or a CAT reporter, the modulation of expression of which gene can be detected via modulation of fluorescence intensity or CAT reporter activity, respectively.

In another example, the subject of detection could be a downstream DEC-205 SV or DCL-1 regulatory target, rather than DEC-205 SV or DCL-1 itself. Yet another example includes DEC-205 SV or DCL-1 binding sites ligated to a minimal reporter. For example, modulation of DEC-205 SV or DCL-1 activity can be detected by screening for the modulation of the functional activity in a Hodgkin and Reed-Sternberg cell or other suitable cell. This is an example of an indirect system where modulation of *DEC-205 SV or DCL-1* expression, *per se*, is not the subject of detection.

These methods provide a mechanism for performing high throughput screening of putative modulatory agents such as the proteinaceous or non-proteinaceous agents comprising synthetic, combinatorial, chemical and natural libraries. These methods will also facilitate the detection of agents which bind either the *DEC-205 SV or DCL-1* nucleic acid molecule or expression product itself or which modulate the expression of an upstream molecule, which upstream molecule subsequently modulates *DEC-205 SV or DCL-1* expression or expression product activity. Accordingly, these methods provide a mechanism for detecting agents which either directly or indirectly modulate DEC-205 SV or DCL-1 expression and/or activity.

The agents which are utilised in accordance with the method of the present invention may take any suitable form. For example, proteinaceous agents may be glycosylated or unglycosylated, phosphorylated or dephosphorylated to various degrees and/or may

contain a range of other molecules used, linked, bound or otherwise associated with the proteins such as amino acids, lipid, carbohydrates or other peptides, polypeptides or proteins. Similarly, the subject non-proteinaceous molecules may also take any suitable form. Both the proteinaceous and non-proteinaceous agents herein described may be linked, bound otherwise associated with any other proteinaceous or non-proteinaceous molecules. For example, in one embodiment of the present invention, said agent is associated with a molecule which permits its targeting to a localised region.

The subject proteinaceous or non-proteinaceous molecule may act either directly or indirectly to modulate the expression of *DEC-205 SV or DCL-1* or the activity of the DEC-205 SV or DCL-1 expression product. Said molecule acts directly if it associates with the *DEC-205 SV or DCL-1* nucleic acid molecule or expression product to modulate expression or activity, respectively. Said molecule acts indirectly if it associates with a molecule other than the *DEC-205 SV or DCL-1* nucleic acid molecule or expression product which other molecule either directly or indirectly modulates the expression or activity of the *DEC-205 SV or DCL-1* nucleic acid molecule or expression product, respectively. Accordingly, the method of the present invention encompasses the regulation of *DEC-205 SV or DCL-1* nucleic acid molecule expression or expression product activity via the induction of a cascade of regulatory steps.

The term "expression" in this context refers to the transcription and translation of a nucleic acid molecule. Reference to "expression product" is a reference to the product produced from the transcription and translation of a nucleic acid molecule.

"Derivatives" of the molecules herein described (for example DEC-205 SV or DCL-1 or other proteinaceous or non-proteinaceous agents) include fragments, parts, portions or variants from either natural or non-natural sources. Non-natural sources include, for example, recombinant or synthetic sources. By "recombinant sources" is meant that the cellular source from which the subject molecule is harvested has been genetically altered. This may occur, for example, in order to increase or otherwise enhance the rate and volume of production by that particular cellular source. Parts or fragments include, for

example, active regions of the molecule. Derivatives may be derived from insertion, deletion or substitution of amino acids. Amino acid insertional derivatives include amino and/or carboxylic terminal fusions as well as intrasequence insertions of single or multiple amino acids. Insertional amino acid sequence variants are those in which one or more amino acid residues are introduced into a predetermined site in the protein although random insertion is also possible with suitable screening of the resulting product. Deletional variants are characterised by the removal of one or more amino acids from the sequence. Substitutional amino acid variants are those in which at least one residue in a sequence has been removed and a different residue inserted in its place. Additions to amino acid sequences include fusions with other peptides, polypeptides or proteins, as detailed above.

Derivatives also include fragments having particular epitopes or parts of the entire protein fused to peptides, polypeptides or other proteinaceous or non-proteinaceous molecules. For example, DEC-205 SV or DCL-1 or derivative thereof may be fused to a molecule to facilitate its homing to a cell. Analogues of the molecules contemplated herein include, but are not limited to, modification to side chains, incorporating of unnatural amino acids and/or their derivatives during peptide, polypeptide or protein synthesis and the use of crosslinkers and other methods which impose conformational constraints on the proteinaceous molecules or their analogues.

Derivatives of nucleic acid sequences which may be utilised in accordance with the method of the present invention may similarly be derived from single or multiple nucleotide substitutions, deletions and/or additions including fusion with other nucleic acid molecules. The derivatives of the nucleic acid molecules utilised in the present invention include oligonucleotides, PCR primers, antisense molecules, molecules suitable for use in cosuppression and fusion of nucleic acid molecules. Derivatives of nucleic acid sequences also include degenerate variants.

A "variant" of DEC-205 SV or DCL-1 should be understood to mean molecules which exhibit at least some of the functional activity of the form of DEC-205 SV or DCL-1 of

which it is a variant. A variation may take any form and may be naturally or non-naturally occurring. A mutant molecule is one which exhibits modified functional activity.

By "homologue" is meant a molecule derived from a species other than human.

Chemical and functional equivalents should be understood as molecules exhibiting any one or more of the functional activities of the subject molecule, which functional equivalents may be derived from any source such as being chemically synthesised or identified via screening processes such as natural product screening. For example chemical or functional equivalents can be designed and/or identified utilising well known methods such as combinatorial chemistry or high throughput screening of recombinant libraries or following natural product screening.

For example, libraries containing small organic molecules may be screened, wherein organic molecules having a large number of specific parent group substitutions are used. A general synthetic scheme may follow published methods (eg., Bunin BA, *et al.* (1994) *Proc. Natl. Acad. Sci. USA, 91:*4708-4712; DeWitt SH, *et al.* (1993) *Proc. Natl. Acad. Sci. USA*, **90**:6909-6913). Briefly, at each successive synthetic step, one of a plurality of different selected substituents is added to each of a selected subset of tubes in an array, with the selection of tube subsets being such as to generate all possible permutation of the different substituents employed in producing the library. One suitable permutation strategy is outlined in US. Patent No. 5,763,263.

There is currently widespread interest in using combinational libraries of random organic molecules to search for biologically active compounds (see for example U.S. Patent No. 5,763,263). Ligands discovered by screening libraries of this type may be useful in mimicking or blocking natural ligands or interfering with the naturally occurring ligands of a biological target. In the present context, for example, they may be used as a starting point for developing analogues which exhibit properties such as more potent pharmacological effects. DEC-205 SV or DCL-1 or a functional part thereof may according to the present invention be used in combination libraries formed by various

solid-phase or solution-phase synthetic methods (see for example U.S. Patent No. 5,763,263 and references cited therein). By use of techniques, such as that disclosed in U.S. Patent No. 5,753,187, millions of new chemical and/or biological compounds may be routinely screened in less than a few weeks. Of the large number of compounds identified, only those exhibiting appropriate biological activity are further analysed.

With respect to high throughput library screening methods, oligomeric or small-molecule library compounds capable of interacting specifically with a selected biological agent, such as a biomolecule, a macromolecule complex, or cell, are screened utilising a combinational library device which is easily chosen by the person of skill in the art from the range of well-known methods, such as those described above. In such a method, each member of the library is screened for its ability to interact specifically with the selected agent. In practising the method, a biological agent is drawn into compound-containing tubes and allowed to interact with the individual library compound in each tube. The interaction is designed to produce a detectable signal that can be used to monitor the presence of the desired interaction. Preferably, the biological agent is present in an aqueous solution and further conditions are adapted depending on the desired interaction. Detection may be performed for example by any well-known functional or non-functional based method for the detection of substances.

In addition to screening for molecules which mimic the activity of DEC-205 SV or DCL-1, it may also be desirable to identify and utilise molecules which function agonistically or antagonistically to DEC-205 SV or DCL-1 in order to up or down-regulate the functional activity of DEC-205 SV or DCL-1 in relation to modulating cell functioning. The use of such molecules is described in more detail below. To the extent that the subject molecule is proteinaceous, it may be derived, for example, from natural or recombinant sources including fusion proteins or following, for example, the screening methods described above. The non-proteinaceous molecule may be, for example, a chemical or synthetic molecule which has also been identified or generated in accordance with the methodology identified above. Accordingly, the present invention contemplates the use of chemical analogues of DEC-205 SV or DCL-1 capable of acting as agonists or antagonists.

Chemical agonists may not necessarily be derived from DEC-205 SV or DCL-1 but may share certain conformational similarities. Alternatively, chemical agonists may be specifically designed to mimic certain physiochemical properties of DEC-205 SV or DCL-1. Antagonists may be any compound capable of blocking, inhibiting or otherwise preventing DEC-205 SV or DCL-1 from carrying out its normal biological functions. Antagonists include monoclonal antibodies specific for DEC-205 SV or DCL-1 or parts of DEC-205 SV or DCL-1.

Analogues of DEC-205 SV or DCL-1 or of DEC-205 SV or DCL-1 agonistic or antagonistic agents contemplated herein include, but are not limited to, modifications to side chains, incorporating unnatural amino acids and/or derivatives during peptide, polypeptide or protein synthesis and the use of crosslinkers and other methods which impose conformational constraints on the analogues. The specific form which such modifications can take will depend on whether the subject molecule is proteinaceous or non-proteinaceous. The nature and/or suitability of a particular modification can be routinely determined by the person of skill in the art.

For example, examples of side chain modifications contemplated by the present invention include modifications of amino groups such as by reductive alkylation by reaction with an aldehyde followed by reduction with NaBH4; amidination with methylacetimidate; acylation with acetic anhydride; carbamoylation of amino groups with cyanate; trinitrobenzylation of amino groups with 2, 4, 6-trinitrobenzene sulphonic acid (TNBS); acylation of amino groups with succinic anhydride and tetrahydrophthalic anhydride; and pyridoxylation of lysine with pyridoxal-5-phosphate followed by reduction with $NaBH_4$.

The guanidine group of arginine residues may be modified by the formation of heterocyclic condensation products with reagents such as 2,3-butanedione, phenylglyoxal and glyoxal.

The carboxyl group may be modified by carbodiimide activation *via* O-acylisourea formation followed by subsequent derivatisation, for example, to a corresponding amide.

Sulphydryl groups may be modified by methods such as carboxymethylation with iodoacetic acid or iodoacetamide; performic acid oxidation to cysteic acid; formation of a mixed disulphides with other thiol compounds; reaction with maleimide, maleic anhydride or other substituted maleimide; formation of mercurial derivatives using 4-chloromercuribenzoate, 4-chloromercuriphenylsulphonic acid, phenylmercury chloride, 2-chloromercuri-4-nitrophenol and other mercurials; carbamoylation with cyanate at alkaline pH.

Tryptophan residues may be modified by, for example, oxidation with N-bromosuccinimide or alkylation of the indole ring with 2-hydroxy-5-nitrobenzyl bromide or sulphenyl halides. Tyrosine residues on the other hand, may be altered by nitration with tetranitromethane to form a 3-nitrotyrosine derivative.

Modification of the imidazole ring of a histidine residue may be accomplished by alkylation with iodoacetic acid derivatives or N-carboethoxylation with diethylpyrocarbonate.

Examples of incorporating unnatural amino acids and derivatives during protein synthesis include, but are not limited to, use of norleucine, 4-amino butyric acid, 4-amino-3-hydroxy-5-phenylpentanoic acid, 6-aminohexanoic acid, t-butylglycine, norvaline, phenylglycine, ornithine, sarcosine, 4-amino-3-hydroxy-6-methylheptanoic acid, 2-thienyl alanine and/or D-isomers of amino acids. A list of unnatural amino acids contemplated herein is shown in Table 2.

TABLE 2

Non-conventional amino acid	Code	Non-conventional amino acid	Code
α-aminobutyric acid	Abu	L-N-methylalanine	Nmala
α-amino-α-methylbutyrate	Mgabu	L-N-methylarginine	Nmarg
aminocyclopropane-carboxylate	Cpro	L-N-methylasparagine	Nmasn
		L-N-methylaspartic acid	Nmasp
aminoisobutyric acid	Aib	L-N-methylcysteine	Nmcys
aminonorbornyl-carboxylate	Norb	L-N-methylglutamine	Nmgln
		L-N-methylglutamic acid	Nmglu
cyclohexylalanine	Chexa	L-N-methylhistidine	Nmhis
cyclopentylalanine	Cpen	L-N-methylisolleucine	Nmile
D-alanine	Dal	L-N-methylleucine	Nmleu
D-arginine	Darg	L-N-methyllysine	Nmlys
D-aspartic acid	Dasp	L-N-methylmethionine	Nmmet
D-cysteine	Dcys	L-N-methylnorleucine	Nmnle
D-glutamine	Dgln	L-N-methylnorvaline	Nmnva
D-glutamic acid	Dglu	L-N-methylornithine	Nmorn
D-histidine	Dhis	L-N-methylphenylalanine	Nmphe
D-isoleucine	Dile	L-N-methylproline	Nmpro
D-leucine	Dleu	L-N-methylserine	Nmser
D-lysine	Dlys	L-N-methylthreonine	Nmthr
D-methionine	Dmet	L-N-methyltryptophan	Nmtrp
D-ornithine	Dorn	L-N-methyltyrosine	Nmtyr
D-phenylalanine	Dphe	L-N-methylvaline	Nmval
D-proline	Dpro	L-N-methylethylglycine	Nmetg
D-serine	Dser	L-N-methyl-t-butylglycine	Nmtbug
D-threonine	Dthr	L-norleucine	Nle
D-tryptophan	Dtrp	L-norvaline	Nva
D-tyrosine	Dtyr	α-methyl-aminoisobutyrate	Maib
D-valine	Dval	α-methyl- -aminobutyrate	Mgabu

	D-α-methylalanine	Dmala	α-methylcyclohexylalanine	Mchexa
	D-α-methylarginine	Dmarg	α-methylcylcopentylalanine	Mcpen
	D-α-methylasparagine	Dmasn	α-methyl-α-napthylalanine	Manap
	D-α-methylaspartate	Dmasp	α-methylpenicillamine	Mpen
5	D-α-methylcysteine	Dmcys	N-(4-aminobutyl)glycine	Nglu
	D-α-methylglutamine	Dmgln	N-(2-aminoethyl)glycine	Naeg
	D-α-methylhistidine	Dmhis	N-(3-aminopropyl)glycine	Norn
	D-α-methylisoleucine	Dmile	N-amino-α-methylbutyrate	Nmaabu
	D-α-methylleucine	Dmleu	α-napthylalanine	Anap
10	D-α-methyllysine	Dmlys	N-benzylglycine	Nphe
	D-α-methylmethionine	Dmmet	N-(2-carbamylethyl)glycine	Ngln
	D-α-methylornithine	Dmorn	N-(carbamylmethyl)glycine	Nasn
	D-α-methylphenylalanine	Dmphe	N-(2-carboxyethyl)glycine	Nglu
	D-α-methylproline	Dmpro	N-(carboxymethyl)glycine	Nasp
15	D-α-methylserine	Dmser	N-cyclobutylglycine	Ncbut
	D-α-methylthreonine	Dmthr	N-cycloheptylglycine	Nchep
	D-α-methyltryptophan	Dmtrp	N-cyclohexylglycine	Nchex
	D-α-methyltyrosine	Dmty	N-cyclodecylglycine	Ncdec
	D-α-methylvaline	Dmval	N-cylcododecylglycine	Ncdod
20	D-N-methylalanine	Dnmala	N-cyclooctylglycine	Ncoct
	D-N-methylarginine	Dnmarg	N-cyclopropylglycine	Ncpro
	D-N-methylasparagine	Dnmasn	N-cycloundecylglycine	Ncund
	D-N-methylaspartate	Dnmasp	N-(2,2-diphenylethyl)glycine	Nbhm
	D-N-methylcysteine	Dnmcys	N-(3,3-diphenylpropyl)glycine	Nbhe
25	D-N-methylglutamine	Dnmgln	N-(3-guanidinopropyl)glycine	Narg
	D-N-methylglutamate	Dnmglu	N-(1-hydroxyethyl)glycine	Nthr
	D-N-methylhistidine	Dnmhis	N-(hydroxyethyl))glycine	Nser
	D-N-methylisoleucine	Dnmile	N-(imidazolylethyl))glycine	Nhis
	D-N-methylleucine	Dnmleu	N-(3-indolylyethyl)glycine	Nhtrp
30	D-N-methyllysine	Dnmlys	N-methyl-γ-aminobutyrate	Nmgabu
	N-methylcyclohexylalanine	Nmchexa	D-N-methylmethionine	Dnmmet
	D-N-methylornithine	Dnmorn	N-methylcyclopentylalanine	Nmcpen
	N-methylglycine	Nala	D-N-methylphenylalanine	Dnmphe

	N-methylaminoisobutyrate	Nmaib	D-N-methylproline	Dnmpro
	N-(1-methylpropyl)glycine	Nile	D-N-methylserine	Dnmser
	N-(2-methylpropyl)glycine	Nleu	D-N-methylthreonine	Dnmthr
	D-N-methyltryptophan	Dnmtrp	N-(1-methylethyl)glycine	Nval
5	D-N-methyltyrosine	Dnmtyr	N-methyla-napthylalanine	Nmanap
	D-N-methylvaline	Dnmval	N-methylpenicillamine	Nmpen
	γ-aminobutyric acid	Gabu	N-(*p*-hydroxyphenyl)glycine	Nhtyr
	L-*t*-butylglycine	Tbug	N-(thiomethyl)glycine	Ncys
	L-ethylglycine	Etg	penicillamine	Pen
10	L-homophenylalanine	Hphe	L-α-methylalanine	Mala
	L-α-methylarginine	Marg	L-α-methylasparagine	Masn
	L-α-methylaspartate	Masp	L-α-methyl-*t*-butylglycine	Mtbug
	L-α-methylcysteine	Mcys	L-methylethylglycine	Metg
	L-α-methylglutamine	Mgln	L-α-methylglutamate	Mglu
15	L-α-methylhistidine	Mhis	L-α-methylhomophenylalanine	Mhphe
	L-α-methylisoleucine	Mile	N-(2-methylthioethyl)glycine	Nmet
	L-α-methylleucine	Mleu	L-α-methyllysine	Mlys
	L-α-methylmethionine	Mmet	L-α-methylnorleucine	Mnle
	L-α-methylnorvaline	Mnva	L-α-methylornithine	Morn
20	L-α-methylphenylalanine	Mphe	L-α-methylproline	Mpro
	L-α-methylserine	Mser	L-α-methylthreonine	Mthr
	L-α-methyltryptophan	Mtrp	L-α-methyltyrosine	Mtyr
	L-α-methylvaline	Mval	L-N-methylhomophenylalanine	Nmhphe
	N-(N-(2,2-diphenylethyl)	Nnbhm	N-(N-(3,3-diphenylpropyl)	Nnbhe
25	carbamylmethyl)glycine		carbamylmethyl)glycine	
	1-carboxy-1-(2,2-diphenyl-	Nmbc		
	ethylamino)cyclopropane			

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30 Crosslinkers can be used, for example, to stabilise 3D conformations, using homo-bifunctional crosslinkers such as the bifunctional imido esters having (CH2)n spacer

groups with n=1 to n=6, glutaraldehyde, N-hydroxysuccinimide esters and hetero-bifunctional reagents which usually contain an amino-reactive moiety.

These types of modifications may be important to stabilise the molecule if administered to an individual or for use as a diagnostic reagent.

The present invention further contemplates analogues capable of acting as antagonists or agonists of the native amino acid or nucleic acid molecules or which can act as functional analogues of the native molecules (herein referred to as an "antagonist" or an "agonist"). Analogues, antagonists and agonists may not necessarily be derived from the subject molecules but may share certain conformational similarities. Alternatively, analogues, antagonists and agonists may be specifically designed to mimic certain physiochemical properties of the molecules. Analogues, antagonists and agonists may be chemically synthesised or may be detected following, for example, natural product screening.

Derivatives also extend to fragments having particular epitopes or parts of the entire molecule fused to peptides, polypeptides or other proteins. The derivatives of the nucleic acid molecules of the present invention include oligonucleotides, PCR primers, antisense molecules, molecules suitable for use in cosuppression and fusion of nucleic acid molecules.

An "effective amount" means an amount necessary at least partly to attain the desired immune response, or to delay the onset or inhibit progression or halt altogether, the onset or progression of a particular condition being treated. The amount varies depending upon the health and physical condition of the individual to be treated, the taxonomic group of individual to be treated, the degree of protection desired, the formulation of the composition, the assessment of the medical situation, and other relevant factors. It is expected that the amount will fall in a relatively broad range that can be determined through routine trials.

It should be understood that the target cell which is treated according to the method of the present invention may be located *ex vivo* or *in vivo*. By "*ex vivo*" is meant that the cell has been removed from the body of a subject wherein the modulation of its activity will be achieved *in vitro*. In accordance with the preferred aspect of the present invention, the cell may be a neoplastic cell, such as a Hodgkin and Reed-Sternberg cell, located *in vivo* and the down-regulation of its growth will be achieved by applying the method of the present invention *in vivo*.

It should be understood that the reference to a "cell" in the context of the present invention is a reference to any form or type of cell, irrespective of its origin. For example, the cell may be a naturally occurring normal or abnormal cell or it may be manipulated, modified or otherwise treated either *in vitro* or *in vivo* such as a cell which has been freeze/thawed or genetically, biochemically or otherwise modified either *in vitro* or *in vivo* (including, for example, cells which are the result of the fusion of two distinct cell types).

A further aspect of the present invention relates to the use of the invention in relation to the treatment and/or prophylaxis of disease conditions characterised by aberrant, unwanted or inappropriate functioning of DEC-205 SV or DCL-1. Still further, the present invention is particularly useful, but in no way limited to, use in the treatment of Hodgkin's lymphoma which is characterised by the Hodgkin and Reed-Sternberg cells which express DEC-205 SV.

The present invention therefore contemplates a method for the treatment and/or prophylaxis of a condition characterised by aberrant, unwanted or otherwise inappropriate functioning of DEC-205 SV or DCL-1 in a subject, said method comprising administering to said subject an effective amount of an agent as hereinbefore defined for a time and under conditions sufficient to modulate the expression of *DEC-205 SV or DCL-1* and/or functioning of DEC-205 SV or DCL-1.

Reference to "aberrant, unwanted or otherwise inappropriate" activity should be understood as a reference to overactivity, underactivity or to physiologically normal activity which is inappropriate in that it is unwanted.

In yet another aspect, the present invention provides a means of targeting a therapeutic treatment method to Hodgkin's lymphoma cells on the basis of their unique expression of the DEC-205 SV expression product. In particular, the unique expression of this molecule by the Hodgkin and Reed-Sternberg malignant cells provides a means for targeting therapeutic means such as immunological cytolytic means (eg. cytotoxic T cell or antibody) or cytotoxic means such as those characterised by the use of chemotherapeutic agents.

According to this aspect of the present invention there is provided a method for the treatment of Hodgkin's lymphoma in a mammal, said method comprising administering to said mammal an effective amount of a cytolytic and/or cytotoxic agent which agent interacts or otherwise associates with DEC-205 SV, for a time and under conditions sufficient for said agent to lyse, apoptose or otherwise kill Hodgkin and Reed-Sternberg cells.

The subject of the treatment or prophylaxis is generally a mammal such as but not limited to human, primate, livestock animal (e.g. sheep, cow, horse, donkey, pig), companion animal (e.g. god, cat), laboratory test animal (e.g. mouse, rabbit, rat, guinea pig, hamster), captive wild animal (e.g. fox, deer). Preferably the mammal is a human or primate. Most preferably the mammal is a human. Although the present invention is exemplified using a murine model, this is not intended as a limitation on the application of the present invention to other species, in particular, human.

Reference herein to "treatment" and "prophylaxis" is to be considered in its broadest context. The term "treatment" does not necessarily imply that a subject is treated until total recovery. Similarly, "prophylaxis" does not necessarily mean that the subject will not eventually contract a disease condition. Accordingly, treatment and prophylaxis include

amelioration of the symptoms of a particular condition or preventing or otherwise reducing the risk of developing a particular condition. The term "prophylaxis" may be considered as reducing the severity or onset of a particular condition. "Treatment" may also reduce the severity of an existing condition.

Administration of the agent in the form of a pharmaceutical composition, may be performed by any convenient means. The modulatory agent of the pharmaceutical composition is contemplated to exhibit therapeutic activity when administered in an amount which depends on the particular case. The variation depends, for example, on the human or animal and the modulatory agent chosen. A broad range of doses may be applicable. Considering a patient, for example, from about 0.1 mg to about 1 mg of modulatory agent may be administered per kilogram of body weight per day. Dosage regimes may be adjusted to provide the optimum therapeutic response. For example, several divided doses may be administered daily, weekly, monthly or other suitable time intervals or the dose may be proportionally reduced as indicated by the exigencies of the situation.

The modulatory agent may be administered in a convenient manner such as by the oral, intravenous (where water soluble), intraperitoneal, intramuscular, subcutaneous, intradermal or suppository routes or implanting (e.g. using slow release molecules). The modulatory agent may be administered in the form of pharmaceutically acceptable nontoxic salts, such as acid addition salts or metal complexes, e.g. with zinc, iron or the like (which are considered as salts for purposes of this application). Illustrative of such acid addition salts are hydrochloride, hydrobromide, sulphate, phosphate, maleate, acetate, citrate, benzoate, succinate, malate, ascorbate, tartrate and the like. If the active ingredient is to be administered in tablet form, the tablet may contain a binder such as tragacanth, corn starch or gelatin; a disintegrating agent, such as alginic acid; and a lubricant, such as magnesium stearate.

In accordance with these methods, the agent defined in accordance with the present invention may be coadministered with one or more other compounds or molecules. By

"coadministered" is meant simultaneous administration in the same formulation or in two different formulations via the same or different routes or sequential administration by the same or different routes. By "sequential" administration is meant a time difference of from seconds, minutes, hours or days between the administration of the two types of molecules. These molecules may be administered in any order.

In another aspect, the present invention contemplates a pharmaceutical composition comprising a modulatory agent as hereinbefore defined and one or more pharmaceutically acceptable carriers and/or diluents. Said modulatory agents are referred to as the active ingredients.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion or may be in the form of a cream or other form suitable for topical application. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol and liquid polyethylene glycol, and the like), suitable mixtures thereof, and vegetable oils. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of superfactants. The preventions of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions are prepared by incorporating the active compounds in the required amount in the appropriate solvent with various of the other ingredients

enumerated above, as required, followed by filtered sterilisation. Generally, dispersions are prepared by incorporating the various sterilised active ingredient into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and the freeze-drying technique which yield a powder of the active ingredient plus any additional desired ingredient from previously sterile-filtered solution thereof.

When the active ingredients are suitably protected they may be orally administered, for example, with an inert diluent or with an assimilable edible carrier, or it may be enclosed in hard or soft shell gelatin capsule, or it may be compressed into tablets, or it may be incorporated directly with the food of the diet. For oral therapeutic administration, the active compound may be incorporated with excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. Such compositions and preparations should contain at least 1% by weight of active compound. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 5 to about 80% of the weight of the unit. The amount of active compound in such therapeutically useful compositions in such that a suitable dosage will be obtained. Preferred compositions or preparations according to the present invention are prepared so that an oral dosage unit form contains between about 0.1 μg and 2000 mg of active compound.

The tablets, troches, pills, capsules and the like may also contain the components as listed hereafter: a binder such as gum, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, lactose or saccharin may be added or a flavouring agent such as peppermint, oil of wintergreen, or cherry flavouring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets, pills, or capsules may be coated with shellac, sugar or both. A syrup or

elixir may contain the active compound, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavouring such as cherry or orange flavour. Of course, any material used in preparing any dosage unit form should be pharmaceutically pure and substantially non-toxic in the amounts employed. In addition, the active compound(s) may be incorporated into sustained-release preparations and formulations.

The pharmaceutical composition may also comprise genetic molecules such as a vector capable of transfecting target cells where the vector carries a nucleic acid molecule encoding a modulatory agent. The vector may, for example, be a viral vector.

Yet another aspect of the present invention relates to modulatory agents, as hereinbefore defined, when used in the method of the present invention.

Still another aspect of the present invention is directed to antibodies to DEC-205 SV or DCL-1 including catalytic antibodies. Such antibodies may be monoclonal or polyclonal and may be selected from naturally occurring antibodies to DEC-205 SV or DCL-1 or may be specifically raised to DEC-205 SV or DCL-1. In the case of the latter, DEC-205 SV or DCL-1 may first need to be associated with a carrier molecule. The antibodies and/or recombinant DEC-205 SV or DCL-1 of the present invention are particularly useful as therapeutic or diagnostic agents. Alternatively, fragments of antibodies may be used such as Fab fragments. Furthermore, the present invention extends to recombinant and synthetic antibodies and to antibody hybrids. A "synthetic antibody" is considered herein to include fragments and hybrids of antibodies. The antibodies of this aspect of the present invention are particularly useful for immunotherapy and may also be used as a diagnostic tool for assessing apoptosis or monitoring the program of a therapeutic regime. For example, DEC-205 SV or DCL-1 can be used to screen for naturally occurring antibodies to DEC-205 SV .

In another example, specific antibodies can be used to screen for DEC-205 SV or DCL-1 proteins. The latter would be important, for example, as a means for screening for levels of DEC-205 SV or DCL-1 in a cell extract or other biological fluid or purifying DEC-205

SV or DCL-1 made by recombinant means from culture supernatant fluid. Techniques for the assays contemplated herein are known in the art and include, for example, sandwich assays, ELISA and flow cytometry.

Both polyclonal and monoclonal antibodies are obtainable by immunization with the protein or peptide derivatives and either type is utilizable for immunoassays. The methods of obtaining both types of sera are well known in the art. Polyclonal sera are less preferred but are relatively easily prepared by injection of a suitable laboratory animal with an effective amount of DEC-205 SV or DCL-1, or antigenic parts thereof, collecting serum from the animal, and isolating specific sera by any of the known immunoadsorbent techniques. Although antibodies produced by this method are utilizable in virtually any type of immunoassay, they are generally less favoured because of the potential heterogeneity of the product.

The use of monoclonal antibodies in an immunoassay is particularly preferred because of the ability to produce them in large quantities and the homogeneity of the product. The preparation of hybridoma cell lines for monoclonal antibody production derived by fusing an immortal cell line and lymphocytes sensitized against the immunogenic preparation can be done by techniques which are well known to those who are skilled in the art. (See, for example Douillard and Hoffman, Basic Facts about Hybridomas, in *Compendium of Immunology* Vol II, ed. by Schwartz, 1981; Kohler and Milstein, *Nature 256*: 495-499, 1975; *European Journal of Immunology 6*: 511-519, 1976).

In another aspect, the molecules of the present invention are also useful as screening targets for use in applications such as the diagnosis of disorders characterised by the expression of DEC-205 SV or DCL-1. For example, screening for the levels of DEC-205 SV protein or *DEC-205 SV* mRNA transcripts in tissues as an indicator of a predisposition to, or the development of, Hodgkin's lymphoma. More specifically, there is now provided a means for screening individuals for the presence of DEC-205 SV encoding nucleic acid molecules or expression product or the specific forms of DEC-205 SV which are transcribed and/or translated by a given population of cells. The screening methodology

may be directed to qualitative and/or quantitative DEC-205 SV analysis.

Accordingly, yet another aspect of the present invention contemplates a method of monitoring a disease condition in a mammal, which disease condition is characterised by DEC-205 SV cellular expression, said method comprising screening for DEC-205 SV and/or *DEC-205 SV* in a biological sample isolated from said mammal.

Screening for DEC-205 SV or *DEC-205 SV* (or DCL-1 to the extent that it may prove to be a useful diagnostic marker) in a biological sample can be performed by any one of a number of suitable methods which are well known to those skilled in the art. Examples of suitable methods include, but are not limited to, *in situ* hybridisation of biopsy sections to detect mRNA transcript or DNA, Northern blotting, RT-PCR of specimens isolated from tissue biopsies or antibody screening of tissue sections.

To the extent that antibody based methods of diagnosis are used, the presence of *DEC-205 SV* or DEC-205 SV may be determined in a number of ways such as by Western blotting, ELISA or flow cytometry procedures. These, of course, include both single-site and two-site or "sandwich" assays of the non-competitive types, as well as in the traditional competitive binding assays. These assays also include direct binding of a labelled antibody to a target.

Sandwich assays are among the most useful and commonly used assays and are favoured for use in the present invention. A number of variations of the sandwich assay technique exist, and all are intended to be encompassed by the present invention. Briefly, in a typical forward assay, an unlabelled antibody is immobilized on a solid substrate and the sample to be tested brought into contact with the bound molecule. After a suitable period of incubation, for a period of time sufficient to allow formation of an antibody-antigen complex, a second antibody specific to the antigen, labelled with a reporter molecule capable of producing a detectable signal is then added and incubated, allowing time sufficient for the formation of another complex of antibody-antigen-labelled antibody. Any unreacted material is washed away, and the presence of the antigen is determined by

observation of a signal produced by the reporter molecule. The results may either be qualitative, by simple observation of the visible signal, or may be quantitated by comparing with a control sample containing known amounts of hapten. Variations on the forward assay include a simultaneous assay, in which both sample and labelled antibody are added simultaneously to the bound antibody. These techniques are well known to those skilled in the art, including any minor variations as will be readily apparent. In accordance with the present invention the sample is one which might contain DEC-205 SV including cell extract, tissue biopsy or possibly serum, saliva, mucosal secretions, lymph, tissue fluid and respiratory fluid. The sample is, therefore, generally a biological sample comprising biological fluid but also extends to fermentation fluid and supernatant fluid such as from a cell culture.

In the typical forward sandwich assay, a first antibody having specificity for the DEC-205 SV or antigenic parts thereof, is either covalently or passively bound to a solid surface. The solid surface is typically glass or a polymer, the most commonly used polymers being cellulose, polyacrylamide, nylon, polystyrene, polyvinyl chloride or polypropylene. The solid supports may be in the form of tubes, beads, discs of microplates, or any other surface suitable for conducting an immunoassay. The binding processes are well-known in the art and generally consist of cross-linking covalently binding or physically adsorbing, the polymer-antibody complex is washed in preparation for the test sample. An aliquot of the sample to be tested is then added to the solid phase complex and incubated for a period of time sufficient (e.g. 2-40 minutes) and under suitable conditions (e.g. 25°C) to allow binding of any subunit present in the antibody. Following the incubation period, the antibody subunit solid phase is washed and dried and incubated with a second antibody specific for a portion of the hapten. The second antibody is linked to a reporter molecule which is used to indicate the binding of the second antibody to the hapten.

An alternative method involves immobilizing the target molecules in the biological sample and then exposing the immobilized target to specific antibody which may or may not be labelled with a reporter molecule. Depending on the amount of target and the strength of the reporter molecule signal, a bound target may be detectable by direct labelling with the

antibody. Alternatively, a second labelled antibody, specific to the first antibody is exposed to the target-first antibody complex to form a target-first antibody-second antibody tertiary complex. The complex is detected by the signal emitted by the reporter molecule.

By "reporter molecule" as used in the present specification, is meant a molecule which, by its chemical nature, provides an analytically identifiable signal which allows the detection of antigen-bound antibody. Detection may be either qualitative or quantitative. The most commonly used reporter molecules in this type of assay are either enzymes, fluorophores or radionuclide containing molecules (i.e. radioisotopes) and chemiluminescent molecules.

In the case of an enzyme immunoassay, an enzyme is conjugated to the second antibody, generally by means of glutaraldehyde or periodate. As will be readily recognized, however, a wide variety of different conjugation techniques exist, which are readily available to the skilled artisan. Commonly used enzymes include horseradish peroxidase, glucose oxidase, beta-galactosidase and alkaline phosphatase, amongst others. The substrates to be used with the specific enzymes are generally chosen for the production, upon hydrolysis by the corresponding enzyme, of a detectable color change. Examples of suitable enzymes include alkaline phosphatase and peroxidase. It is also possible to employ fluorogenic substrates, which yield a fluorescent product rather than the chromogenic substrates noted above. In all cases, the enzyme-labelled antibody is added to the first antibody hapten complex, allowed to bind, and then the excess reagent is washed away. A solution containing the appropriate substrate is then added to the complex of antibody-antigen-antibody. The substrate will react with the enzyme linked to the second antibody, giving a qualitative visual signal, which may be further quantitated, usually spectrophotometrically, to give an indication of the amount of hapten which was present in the sample. "Reporter molecule" also extends to use of cell agglutination or inhibition of agglutination such as red blood cells on latex beads, and the like.

Alternately, fluorescent compounds, such as fluorecein and rhodamine, may be chemically coupled to antibodies without altering their binding capacity. When activated by

illumination with light of a particular wavelength, the fluorochrome-labelled antibody adsorbs the light energy, inducing a state to excitability in the molecule, followed by emission of the light at a characteristic color visually detectable with a light microscope. As in the EIA, the fluorescent labelled antibody is allowed to bind to the first antibody-hapten complex. After washing off the unbound reagent, the remaining tertiary complex is then exposed to the light of the appropriate wavelength the fluorescence observed indicates the presence of the hapten of interest. Immunofluorescene and EIA techniques are both very well established in the art and are particularly preferred for the present method. However, other reporter molecules, such as radioisotope, chemiluminescent or bioluminescent molecules, may also be employed.

Further features of the present invention are more fully described in the following non-limiting examples.

TABLE 4

SEQ ID NO	SEQUENCE DESCRIPTION
<400>1	Human DEC205/DCL-1 splice variant (exon 34 fusion): cDNA sequence
<400>2	Human DEC205/DCL-1 splice variant (exon 34 fusion): amino acid sequence
<400>3	Human DEC205/DCL-1 splice variant (exon 34 fusion): complementary DNA strand
<400>4	Human DCL-1 cDNA sequence
<400>5	Human DCL-1 amino acid sequence
<400>6	Human DCL-1 complementary DNA sequence
<400>7	Murine DCL-1 cDNA sequence
<400>8	Murine DCL-1 amino acid sequence
<400>9	Murine DCL-1 complementary DNA sequence
<400>10	Rat DCL-1 cDNA sequence
<400>11	Rat DCL-1 amino acid sequence
<400>12	Rat DCL-1 complementary DNA sequence
<400>13	Bovine DCL-1 EST sequence
<400>14	Figure 4 sequence
<400>15	Figure 4 sequence
<400>16	Figure 4 sequence
<400>17	Figure 4 sequence
<400>18	Figure 4 sequence
<400>19	Figure 4 sequence
<400>20	Human DEC-205/DCL-1 cDNA (exon 33 fusion) sequence
<400>21	Human DEC-205/DCL-1 amino acid (exon 33 fusion) sequence
<400>22	Human DEC-205/DCL-1 (exon 33 fusion) complementary DNA strand sequence
<400>23	Primer 62
<400>24	Primer 63

<400>25	Primer 78
<400>26	Primer 85
<400>27	Primer 86
<400>28	Primer 88
<400>29	Primer 90
<400>30	Primer 92
<400>31	Primer 94

EXAMPLE 1

HODGKIN'S LYMPHOMA CELL LINES EXPRESS A FUSION PROTEIN ENCODED BY INTERGENICALLY SPLICE mRNA FOR THE MULTILECTIN RECEPTOR DEC-205 (CD205) AND A NOVEL C-TYPE LECTIN RECEPTOR DCL-1

Cell lines

The human hematopoietic cell lines, HEL, KG-1, K562, THP-1, U937, Mann, Daudi, Raji, WT49, Mann, Molt-4, Jurkat and HSB-2 were obtained from the American Type Culture Collection (Rockville, MD). L428 cells were provided by V. Diehl (Klinik fur Innere Medizin, Cologne, Germany).[23] HDLM-2[24] and KM-H2 cells[25] were obtained from the German Collection of Microorganism and Cell Culture (Braunschweig, Germany). Mono Mac 6 cells[26] were provided by E. M. Schneider (Dusseldorf, Germacy). All cell lines were maintained in RPMI 1640 (Invitrogen, Melbourne, VIC, Australia), 10 % fetal calf serum (FCS, Invitrogen), 100 U/ml penicillin, and 100 μg/ml streptomycin, except for HDLM-2 cells, which were maintained in 20% FCS. These cells were subjected to RNA preparation using TRIzol (Invitrogen) for RT-PCR and Northern blot analysis.

Antibodies and other reagents

The mAb MMRI-7 against human DEC-205 was produced in house.[27] MMRI-7 binds to an epitope within DEC-205 CRD 1 and 2. The other anti human DEC-205 mAb, M335 was provided through the 7th International Workshop on Human Leukocyte Differentiation Antigens. M335 binds to an epitope within DEC-205 cysteine-rich domain (CR).[27]

Goat anti mouse IgG was purchased from Dako (Botany, NSW, Australia). Horse radish perioxidase (HRP)-conjugated goat anti mouse IgG-Fc specific and protein A-conjugated agarose beads were from Sigma (Sydney, NSW, Australia). HRP-conjugated sheep anti rabbit IgG was from Silenus (Melbourne, VIC, Australia). ELISA plates (Maxsorb) were from Nalge Nunc International (Rochester, NY). Prestained protein standards (Benchmark

Prestained Protein Ladder) and DNA ladder (1 kb ladder) were from Invitrogen. Molecular biological enzymes (e.g. restriction enzymes, polymerases and ligase) were obtained from Invitrogen, Promega (Sydney, NSW, Australia) or Roche Applied Science (Castle Hill, NSW, Australia). Unless specified, general chemicals were obtained from Sigma (Castle Hill, NSW, Australia) or BDH (Poole, England).

Rabbit polyclonal peptide antisera against the DEC-205 CP domain and the DCL-1 CP were produced by immunizing New Zealand White rabbits with diphtheria toxoid-conjugated synthetic peptide CEDEIMLPSFHD and CGEENEYPYQFD (Minotopes, Clayton, VIC, Australia), respectively, using a conventional schedule with Freund adjuvant at the Herston Medical Research Institute (Herston, QLD, Australia). To assess the titer of the antibodies against CP peptides, an ELISA plate was coated with streptavidin (Sigma) and biotinylated peptides for DEC-205 CP (biotin-SGSGEDEIMLPSFHD) and DCL-1 CP (biotin-SGSGEENEYPYQFD) captured. The plate was blocked with 1% (w/v) sodium caseinate (Sigma) in PBS and 0.1% (w/v) Tween 20 (PBS/Tw), and incubated with serially diluted antisera. After washing the plate with PBS/Tw, bound antibody was detected with HRP-sheep anti rabbit IgG and *o*-phenylenediamine hydrochloride, and quantitated with 492 nm using an ELISA reader. There was no cross-reactivity detected between these two rabbit CP antibodies at the dilutions used in the experiments described (data not shown).

3'-Rapid amplification of cDNA ends (3'-RACE)

The 3'-end of DEC-205 mRNA was obtained by 3'-RACE was performed as described previously.[17] Briefly, L428 mRNA was reverse transcribed with an oligo dT adaptor primer. The obtained L428 cDNA pool was subjected to PCR using DEC-205 specific forward primer and an adaptor primer, and cloned into pBlueScript SKII (Stratagene, La Jolla, CA). The clones analyzed by restriction enzyme mapping and sequencing using a BigDye Terminator kit on a ABI Prism 377 automated sequencer (PE Applied Biosystems, Scoresby, VIC, Australia) by Australian Genome Research Facility (University of Queensland, St. Lucia, QLD, Australia).

RT-PCR analysis

PCR was performed on the L428 cDNA pool using DEC-205 specific forward primers (078, 088, 090, 092 and 094, nested within various parts of DEC-205 ectodomain) in combination with either DEC-205 specific reverse primer (085, nested within DEC-205 CP) or DCL-1 specific reverse primer (086, nested within DCL-1 ectodomain) with an Expand Long Template PCR system (Roche)(Table 3). The PCR reactions were fractionated in 0.8% agarose in Tris-acetate buffer (40 mM Tris-acetate, 1 mM EDTA, pH 7.6) and visualized with ethidium bromide. The PCR products obtained by the primer combination 078/085 and 078/086 were cloned into pGEM-T Easy vector (Promega) and sequenced.

Northern blot analysis

Approximately 10 μg of total RNA from cultured cell lines was fractionated in formaldehyde-denatured 1% agarose gel, and transferred to Hybond N^+ cationic nylon membrane (Amersham Biosciences, Sydney, NSW, Australia). The 864 bp DEC-205 cDNA probe nested within DEC-205 CRD1 and 2 was PCR amplified using primers 094 and 095 on the DEC-205 cDNA clone pCRD1/2-Ig[27] and Taq polymerase (Roche). The 1617 bp DCL-1 cDNA probe was PCR amplified using DCL-1 specific primers 062 and 063 on the pBS30-1 (Fig 1). These probes were purified using QIAquick PCR Purification kit (Qiagen, Clifton Hill, VIC, Australia) and labeled with [α-^{32}P]dATP (Amersham Biosciences) using Strip-EZ DNA StipAble DNA probe Synthesis and Removal kit (Ambion, Austin, TX). The membrane was hybridized sequentially with these probes and exposed to a Kodak BioMax MS X-ray film at –70°C using an intensifying screen (Amersham Biosciences). The final wash was 0.1 X SSC (1 X SSC is 0.15 M NaCl, 15 mM Na-citrate, pH7.0) and 0.5% SDS at 68°C. After each probing, the membrane was chemically stripped according to the manufacture's instruction, and used for hybridization with the other probes.

Preparation of cell lysate

Approximately 10^7 cells were lysed with 1 ml of 0.15 M NaCl, 25 mM Tris-HCl, pH 7.4, 1% (v/v) Triton X-100, 0.5% (w/v) sodium deoxycholate, 0.1% (w/v) SDS and a cocktail of protease inhibitors (Complete, EDTA-free, Roche Applied Science) and incubated on ice for 10 min with occasional vortexing. After centrifugation at 12,000 x g for 20 min at 4°C, the supernatant was collected and used directly for immunoprecipitation/Western blot or sandwich ELISA analysis described below.

Immunoprecipitation/Western blot analysis

The cell extract was precleared with a non-immune rabbit serum and protein A Sepharose (Sigma) for 1 h at 4°C, and subjected to immunoprecipitation using the rabbit peptide antisera against DEC-205 CP or DCL-1 CP with protein A Sepharose overnight at 4°C. The beads were washed with a wash buffer (0.15 M NaCl, 25 mM Tris-HCl, pH7.5, 0.2% (v/v) Triton X-100 and 0.5% (w/v) sodium deoxycholate), and eluted with SDS-PAGE sample buffer (2 % (w/v) SDS, 62.5 mM Tris-HCl, pH6.8, 0.01% (w/v) bromophenol blue and 10% (v/v) glycerol) by heating at 95°C for 5 min. The samples were subjected to Laemmli discontinuous SDS-PAGE with 10 % (v/v) polyacrylamide separating gel[28] in the non-reducing condition, and transferred to a polyvinylidene fluoride membrane (PVDF-Plus, Osmonics, Westborough, MA). The membrane was blocked with 5% (w/v) non-fat dry milk in PBS/Tw (BLOTTO), incubated with a mixture of DEC-205 mAbs (MMRI-7 and M335, 5 µg/ml each) overnight at 4°C, and washed with PBS/Tw. The membrane was incubated with HRP-anti goat mouse IgG, and the bound enzyme was detected with enhanced chemiluminescence (SuperSignal West Pico, Pierce, Rockford, IL) on a Kodak X-Omat XB-1 X-ray film.

Sandwich ELISA

An ELISA plate was coated with 10 µg/ml goat anti mouse IgG in PBS, washed with PBS/Tw and blocked with BLOTTO. To the plate a mixture of DEC-205 mAb (MMRI-7

and M335, 2 μg/ml each) was added and incubated for 1 h at room temperature. The plate was washed and incubated with the serially diluted cell extracts overnight at 4°C. The plate was washed with PBS/Tw and incubated with either rabbit peptide antibodies against DEC-205 CP or DCL-1 CP (1:1000 dilution in PBS/Tw) or non immune rabbit serum for 1 h at room temperature and after washing with PBS/Tw, the plate was incubated with HRP-conjugated goat anti rabbit IgG in 5% mouse serum and PBS/TW. The plate was developed with o-phenylenediamine dihydrochloride and quantitated at 492 nm.

EXAMPLE 2

IDENTIFICATION OF THE cDNA CLONE ENCODING DEC-205/DCL-1 FUSION

To obtain the 3'-end of human DEC-205 mRNA, we performed 3'-RACE.[17] This resulted in amplification of an ~ 3 kb PCR product (data not shown). When we cloned the PCR product and analyzed several clones by restriction enzyme analysis, however, we realized that there were two distinct sequences within the PCR product. The clone pB30-3 contained the authentic DEC-205 sequence encoding the DEC-205 CRD 8-10, TM and CP[17]. The other clone pB30-1, however, encoded DEC-205 CRD 8-10 followed by a unique sequence distinct from the DEC-205 TM and CP sequence (Figure 1A). The junction of the DEC-205 and unique sequence was located within the connecting region (spacer 11) between the DEC-205 CRD10 and TM. A BLAST search identified the unique sequence as a part of the cDNA, KIAA0022 derived from KG-1 cell cDNA library[22]. Our further analysis showed that the KIAA0022 contained a partial cDNA encoding a novel type I transmembrane C-type lectin receptor, and we termed it, DCL-1 (DEC-205-associated C-type Lectin-1). The complete DCL-1 coding region encodes a signal peptide (SP), one CRD, one TM and one CP. DCL-1 was recently mapped to chromosome band 2q24. More details of DCL-1 will be published elsewhere (in preparation).

The sequence analysis showed that fusion junction occurred within the codon G/GC (/ indicates the junction) for Gly in the DEC-205 spacer 11, connected to the codon G/AC for

Asp in the junction between the DCL-1 SP and CRD. The fusion junction was in-frame, connecting the DEC-205 CRD 10 to the DCL-1 CRD, TM and CP, suggesting that the DEC-205/DCL-1 fusion mRNA is translated. Further, analysis of the DEC-205 and DCL-1 genes indicated that the junction is formed by splicing and fusing DEC-205 exon 34 to DCL-1 exon 2 (described below).

EXAMPLE 3

THE DEC-205/DCL-1 FUSION mRNA APPEARS TO ENCODE THE ENTIRE DEC-205 ECTODOMAIN

We examined L428 cDNA containing the DEC-205/DCL-1 junction by RT-PCR to see whether it included the entire DEC-205 ectodomain (Figure 2). The combination of the DEC-205 CP-specific reverse primer 085 with DEC-205-specific forward primers, nested to various parts of DEC-205 ectodomain, yielded major PCR products of the sizes predicted in accordance with the primer combinations used. We also detected slightly smaller (by 168 bp) minor PCR products, which were most apparent in the primer combinations of 078/085 and 088/085. When the DCL-1-specific reverse primer 086 was used in combination with the same DEC-205-specific forward primers, we detected doublet bands (~200 bp apart). The larger band of which was the predicted size. Sequence analysis indicated that the smaller RT-PCR fragments from DEC-205 itself or the DEC-205/DCL-1 fusion mRNA were amplified from alternatively spliced RNA, lacking DEC-205 exon 34 (described below). Thus, the DEC-205/DCL-1 fusion mRNA encodes the entire DEC-205 ectodomain, but may also lack DEC-205 exon 34 in an alternatively spliced variant.

EXAMPLE 4

THE DEC-205/DCL-1 FUSION mRNA IS PREDOMINANTLY EXPRESSED BY HRS CELL LINES

To assess DEC-205/DCL-1 fusion mRNA expression, we performed Northern blot analysis in several hematopoietic cell lines (Figure 3). The DCL-1-specific probe nested within the DCL-1 ectodomain detected a single 4.2 kb DCL-1 mRNA band in myeloid cell

lines (HEL, HL60, U937 and Monomac 6), but there were no band detected in the B or T cell lines tested. We detected a single 9.5 kb DEC-205/DCL-1mRNA band in HRS cell lines (HDLM-2, L428 and KM-H2),, however, we did not detect the 4.2 kb DCL-1 mRNA band observed in the myeloid cell lines. The U937 appear to express a small amount of the 9.5 kb DEC-205/DCL-1 mRNA in addition to the 4.2 kb DCL-1 mRNA band. When DEC-205-specific probe nested within the CR was used to hybridize the same blot after the DCL-1 probe was stripped, a 7.5 kb DEC-205 mRNA band was detected in myeloid cell lines (HEL and U937), B cell lines (Daudi and Mann) and all HRS cell lines. In addition, we detected a 9.5 kb DEC-205/DCL-1 mRNA band in all HRS cell lines and the U937 as described previously.[17] Thus, it appears that DEC-205/DCL-1 fusion mRNA is predominated in HRS cell lines.

EXAMPLE 5

THE DEC-205 AND DCL-1 GENE ARE JUXTAPOSED IN CHROMOSOME BAND 2Q24

We mapped the DEC-205 gene previously to the chromosome band 2q24.[17] The KIAA0022/DCL-1 gene was previously located to chromosome 2[22] and further mapped recently to the identical chromosomal band in the NCBI UniGene database. Using the NCBI Genome BLAST, we identified the human genomic contig NT 005151 containing both DEC-205 and the DCL-1 gene. Our sequence analysis showed that DEC-205 and DCL-1 genes consist of 35 and 6 exons, respectively, and the DEC-205 gene is localized ~5.4 kb upstream of the DCL-1 gene (Figure 4). Therefore, the DEC-205 and DCL-1 fusion mRNA appears to be generated by cotranscription of both DEC-205 and DCL-1 genes followed by intergenic splicing to remove the DEC-205 exon 35 (or exon 34/35) and DCL-1 exon 1.

EXAMPLE 6

DEC-205/DCL-1 FUSION mRNA IS TRANSLATED TO THE FUSION PROTEIN

We sought to establish whether the DEC-205/DCL-1 fusion mRNA is translated into a fusion protein. We prepared cell lysates from three HRS cell lines (DEC-205 mRNA$^+$, DEC-205/DCL-1 fusion mRNA$^+$), HEL (DEC-205 mRNA$^+$, DEC-205/DCL-1 fusion mRNA$^-$) and Jurkat cell line (DEC-205 mRNA$^-$, DEC-205/DCL-1 fusion mRNA$^-$)(see Figure 3), and subjected them to immunoprecipitation with the DEC-205 CP or DCL-1 CP peptide antisera. The immunoprecipitated samples were further analyzed by Western blot with DEC-205 mAbs to detect DEC-205 and DEC-205/DCL-1 fusion protein in non-reducing conditions (Figure 5A). The DEC-205 CP antiserum precipitated a broad but single ~180 kDa DEC-205 protein band specifically from the three HRS cell lines (L428, HDLM-2 and KM-H2) and HEL cells. There was no detectable signal in Jurkat cells. When the DCL-1 CP antiserum was used for the initial immunoprecipitation, we detected low levels of ~180 kDa DEC-205/DCL-1 fusion protein band in the three HRS cell lines, but not in HEL or Jurkat cells. The presence of this DEC-205/DCL-1 fusion protein band in these HRS cell extracts was not due to cross-reactivity of DCL-1 CP antiserum with DEC-205 CP because (i) there was no cross-reactivity in the DCL-1 CP antiserum with DEC-205 CP peptide assessed by ELISA analysis (data not shown), (ii) 60 times longer exposure of HEL sample did not produce any band (Figure 5A) and (iii) the DCL-1 CP antiserum detected the weakest signal in KM-H2 extracts, which contained most DEC-205 protein (Figure 5A and described below).

To determine the relative abundance of the DEC-205/DCL-1 fusion protein to DEC-205, we developed a sandwich ELISA using the DEC-205 mAbs for capturing and the CP antisera for detection (Figure 5B). The HRS cell lines express most DEC-205 protein (KM-H2 > L428 > HDLM-2), followed by HEL cells. We detected relatively small amounts of the DEC-205/DCL-1 fusion protein in L428 and HDLM-2 cells, approximately 30-50 times less than the amount of DEC-205. No fusion protein was detected in the KM-H2 cells, probably because the amount of KM-H2 derived fusion protein is below the detection limit. The negative control, Jurkat, did not show any signal. The relative

abundance of both DEC-205 and DEC-205/DCL-1 fusion protein by the ELISA correlated with the immunoprecipitation/Western blot data (Figure 5A).

Those skilled in the art will appreciate that the invention described herein is susceptible to variations and modifications other than those specifically described. It is to be understood that the invention includes all such variations and modifications. The invention also includes all of the steps, features, compositions and compounds referred to or indicated in this specification, individually or collectively, and any and all combinations of any two or more of said steps or features.

Table 3. The DNA sequences of oligonucleotides primers used in this study

Primer	Sequence (5'>3')
062	GACCATGGAGCGGACATGATA <400>23
063	GGCTCTACCATCTGGGTTTGT <400>24
078	CCGCCATGTCGCGCGGCCT <400>25
085	ACCAAATCAGTCCGCCCATGAGAA <400>26
086	ATCATGTCCGCTCCATGGTCAGTA <400>27
088	TATTCAGAAGTTAAAAGCAGA <400>28
090	CCAAAAGGCCGTACTCCAAAA <400>29
092	GGAGGAAAACTGAATGACGCA <400>30
094	GAAAACGGTTGTGAAGATAAT <400>31

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DATED this 6th day of December, 2002

THE CORPORATION OF THE TRUSTEES OF THE ORDER OF THE SISTERS OF MERCY IN QUEENSLAND
By its Patent Attorneys
DAVIES COLLISON CAVE

SEQUENCE LISTING

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att acc  atg aga gtt tgg ctt  gga tta tct caa cat  tct gtt gac      4824
Ile Thr  Met Arg Val Trp Leu  Gly Leu Ser Gln His  Ser Val Asp
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cag tct  tgg agt tgg tta gat  gga tca gaa gtg aca  ttt gtc aaa      4869
Gln Ser  Trp Ser Trp Leu Asp  Gly Ser Glu Val Thr  Phe Val Lys
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tgg gaa  aat aaa agt aag agt  ggt gtt gga aga tgt  agc atg ttg      4914
Trp Glu  Asn Lys Ser Lys Ser  Gly Val Gly Arg Cys  Ser Met Leu
    1625                1630                1635

ata gct  tca aat gaa act tgg  aaa aaa gtt gaa tgt  gaa cat ggt      4959
Ile Ala  Ser Asn Glu Thr Trp  Lys Lys Val Glu Cys  Glu His Gly
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ttt gga  aga gtt gtc tgc aaa  gtg cct ctg gac tgt  cct tca tct      5004
Phe Gly  Arg Val Val Cys Lys  Val Pro Leu Asp Cys  Pro Ser Ser
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act tgg  att cag ttc caa gac  agt tgt tac att ttt  ctc caa gaa      5049
Thr Trp  Ile Gln Phe Gln Asp  Ser Cys Tyr Ile Phe  Leu Gln Glu
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gcc atc  aaa gta gaa agc ata  gag gat gtc aga aat  cag tgt act      5094
Ala Ile  Lys Val Glu Ser Ile  Glu Asp Val Arg Asn  Gln Cys Thr
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gac cat  gga gcg gac atg ata  agc ata cat aat gaa  gaa gaa aat      5139
Asp His  Gly Ala Asp Met Ile  Ser Ile His Asn Glu  Glu Glu Asn
    1700                 1705                 1710

gct ttt  ata ctg gat act ttg  aaa aag caa tgg aaa  ggc cca gat      5184
Ala Phe  Ile Leu Asp Thr Leu  Lys Lys Gln Trp Lys  Gly Pro Asp
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gat atc  cta cta ggc atg ttt  tat gac aca gat gat  gcg agt ttc      5229
Asp Ile  Leu Leu Gly Met Phe  Tyr Asp Thr Asp Asp  Ala Ser Phe
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aag tgg  ttt gat aat tca aat  atg aca ttt gat aag  tgg aca gac      5274
Lys Trp  Phe Asp Asn Ser Asn  Met Thr Phe Asp Lys  Trp Thr Asp
    1745                 1750                 1755

caa gat  gat gat gag gat tta  gtt gac acc tgt gct  ttt ctg cac      5319
Gln Asp  Asp Asp Glu Asp Leu  Val Asp Thr Cys Ala  Phe Leu His
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atc aag  aca ggt gaa tgg aaa  aaa gga aat tgt gaa  gtt tct tct      5364
Ile Lys  Thr Gly Glu Trp Lys  Lys Gly Asn Cys Glu  Val Ser Ser
    1775                 1780                 1785

gtg gaa  gga aca cta tgc aaa  aca gct atc cca tac  aaa agg aaa      5409
Val Glu  Gly Thr Leu Cys Lys  Thr Ala Ile Pro Tyr  Lys Arg Lys
    1790                 1795                 1800

tat tta  tca gat aac cac att  tta ata tca gca ttg  gtg att gct      5454
Tyr Leu  Ser Asp Asn His Ile  Leu Ile Ser Ala Leu  Val Ile Ala
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agc acg  gta att ttg aca gtt  ttg gga gca atc att  tgg ttc ctg      5499
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Ser Thr  Val Ile Leu Thr Val  Leu Gly Ala Ile Ile  Trp Phe Leu
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Tyr Lys  Lys His Ser Asp Ser  Arg Phe Thr Thr Val  Phe Ser Thr
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gca ccc  caa tca cct tat aat  gaa gac tgt gtt ttg  gta gtt gga      5589
Ala Pro  Gln Ser Pro Tyr Asn  Glu Asp Cys Val Leu  Val Val Gly
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Asn Asp Pro Phe Thr Ile Val His Gly Asn Thr Gly Lys Cys Ile Lys
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Pro Val Tyr Gly Trp Ile Val Ala Asp Asp Cys Asp Glu Thr Glu Asp
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Lys Leu Trp Lys Trp Val Ser Gln His Arg Leu Phe His Leu His Ser
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Gln Lys Cys Leu Gly Leu Asp Ile Thr Lys Ser Val Asn Glu Leu Arg
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Met Phe Ser Cys Asp Ser Ser Ala Met Leu Trp Trp Lys Cys Glu His
100 105 110

His Ser Leu Tyr Gly Ala Ala Arg Tyr Arg Leu Ala Leu Lys Asp Gly
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His Gly Thr Ala Ile Ser Asn Ala Ser Asp Val Trp Lys Lys Gly Gly
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Ser Glu Glu Ser Leu Cys Asp Gln Pro Tyr His Glu Ile Tyr Thr Arg
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Asp Gly Asn Ser Tyr Gly Arg Pro Cys Glu Phe Pro Phe Leu Ile Asp
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Gly Thr Trp His His Asp Cys Ile Leu Asp Glu Asp His Ser Gly Pro
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Trp Cys Ala Thr Thr Leu Asn Tyr Glu Tyr Asp Arg Lys Trp Gly Ile
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Cys Leu Lys Pro Glu Asn Gly Cys Glu Asp Asn Trp Glu Lys Asn Glu

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Gln Phe Gly Ser Cys Tyr Gln Phe Asn Thr Gln Thr Ala Leu Ser Trp
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Lys Glu Ala Tyr Val Ser Cys Gln Asn Gln Gly Ala Asp Leu Leu Ser
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Ile Asn Ser Ala Ala Glu Leu Thr Tyr Leu Lys Glu Lys Glu Gly Ile
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Ala Lys Ile Phe Trp Ile Gly Leu Asn Gln Leu Tyr Ser Ala Arg Gly
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Trp Glu Trp Ser Asp His Lys Pro Leu Asn Phe Leu Asn Trp Asp Pro
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Asp Arg Pro Ser Ala Pro Thr Ile Gly Gly Ser Ser Cys Ala Arg Met
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Asp Ala Glu Ser Gly Leu Trp Gln Ser Phe Ser Cys Glu Ala Gln Leu
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Pro Tyr Val Cys Arg Lys Pro Leu Asn Asn Thr Val Glu Leu Thr Asp
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Val Trp Thr Tyr Ser Asp Thr Arg Cys Asp Ala Gly Trp Leu Pro Asn
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Asn Gly Phe Cys Tyr Leu Leu Val Asn Glu Ser Asn Ser Trp Asp Lys
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Ala His Ala Lys Cys Lys Ala Phe Ser Ser Asp Leu Ile Ser Ile His
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Ser Leu Ala Asp Val Glu Val Val Val Thr Lys Leu His Asn Glu Asp
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Ile Lys Glu Glu Val Trp Ile Gly Leu Lys Asn Ile Asn Ile Pro Thr
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Leu Phe Gln Trp Ser Asp Gly Thr Glu Val Thr Leu Thr Tyr Trp Asp
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Glu Asn Glu Pro Asn Val Pro Tyr Asn Lys Thr Pro Asn Cys Val Ser
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Thr Cys Tyr Lys Ile Tyr Glu Asp Glu Val Pro Phe Gly Thr Asn Cys

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Asp Pro Cys Pro Glu Gly Trp Gln Ser Phe Pro Ala Ser Leu Ser Cys
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Tyr Lys Val Phe His Ala Glu Arg Ile Val Arg Lys Arg Asn Trp Glu
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Ser His Val Asp Glu Ile Lys Glu Phe Leu His Phe Leu Thr Asp Gln
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Phe Ser Gly Gln His Trp Leu Trp Ile Gly Leu Asn Lys Arg Ser Pro
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Ala Ala Val Lys Val Phe His Arg Pro Trp Arg Arg Gly Trp His Phe
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Tyr Asp Asp Arg Glu Phe Ile Tyr Leu Arg Pro Phe Ala Cys Asp Thr
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Lys Leu Glu Trp Val Cys Gln Ile Pro Lys Gly Arg Thr Pro Lys Thr
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Pro Asp Trp Tyr Asn Pro Asp Arg Ala Gly Ile His Gly Pro Pro Leu
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Leu Ile Asp Leu Gly Lys Pro Thr Asp Cys Ser Thr Lys Leu Pro Phe
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Ser Ala Ala Lys Val Gln Cys Ser Glu Gln Trp Ile Pro Phe Gln Asn
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Gln Ile Glu Gln Asp Phe Ile Thr Ser Leu Leu Pro Asp Met Glu Ala
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Thr Leu Trp Ile Gly Leu Arg Trp Thr Ala Tyr Glu Lys Ile Asn
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Val Asp Ser Val Lys Cys Pro Ser Pro Val Leu Asn Thr Pro Trp
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Met Pro Tyr Glu Asp Gly Ile Tyr Ser Val Ile Gln Lys Lys Val

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Ile Val Lys Arg Asp Gly Phe Pro Leu Trp Val Gly Leu Ser Ser
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Phe Asp Tyr Ile Pro Trp Lys Gly Gln Thr Ser Pro Gly Asn Cys
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Ser Lys His Asp His Ser Ala Thr Ile Val Ser Ile Lys Asp Glu
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Ile Thr Met Arg Val Trp Leu Gly Leu Ser Gln His Ser Val Asp
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Gln Ser Trp Ser Trp Leu Asp Gly Ser Glu Val Thr Phe Val Lys
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Phe Gly Arg Val Val Cys Lys Val Pro Leu Asp Cys Pro Ser Ser
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Asp His Gly Ala Asp Met Ile Ser Ile His Asn Glu Glu Glu Asn
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Ile Lys Thr Gly Glu Trp Lys Lys Gly Asn Cys Glu Val Ser Ser
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Val Glu Gly Thr Leu Cys Lys Thr Ala Ile Pro Tyr Lys Arg Lys
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Tyr Leu Ser Asp Asn His Ile Leu Ile Ser Ala Leu Val Ile Ala
1805 1810 1815

Ser Thr Val Ile Leu Thr Val Leu Gly Ala Ile Ile Trp Phe Leu
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Tyr Lys Lys His Ser Asp Ser Arg Phe Thr Thr Val Phe Ser Thr
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Ala Leu Pro Ala Leu Leu Leu Pro Leu Leu Gly Leu Ala Ala Ala Ala
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Val Ala Asp Cys Pro Ser Ser Thr Trp Ile Gln Phe Gln Asp Ser Cys
25 30 35

tac att ttt ctc caa gaa gcc atc aaa gta gaa agc ata gag gat gtc 200
Tyr Ile Phe Leu Gln Glu Ala Ile Lys Val Glu Ser Ile Glu Asp Val
40 45 50

aga aat cag tgt act gac cat gga gcg gac atg ata agc ata cat aat 248
Arg Asn Gln Cys Thr Asp His Gly Ala Asp Met Ile Ser Ile His Asn
55 60 65

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Glu Glu Glu Asn Ala Phe Ile Leu Asp Thr Leu Lys Lys Gln Trp Lys
70 75 80

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Gly Pro Asp Asp Ile Leu Leu Gly Met Phe Tyr Asp Thr Asp Asp Ala
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Ser Phe Lys Trp Phe Asp Asn Ser Asn Met Thr Phe Asp Lys Trp Thr
105 110 115

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Asp Gln Asp Asp Asp Glu Asp Leu Val Asp Thr Cys Ala Phe Leu His
120 125 130

atc aag aca ggt gaa tgg aaa aaa gga aat tgt gaa gtt tct tct gtg 488
Ile Lys Thr Gly Glu Trp Lys Lys Gly Asn Cys Glu Val Ser Ser Val
135 140 145

gaa gga aca cta tgc aaa aca gct atc cca tac aaa agg aaa tat tta 536

Glu Gly Thr Leu Cys Lys Thr Ala Ile Pro Tyr Lys Arg Lys Tyr Leu
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230

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35 40 45

Ile Glu Asp Val Arg Asn Gln Cys Thr Asp His Gly Ala Asp Met Ile
50 55 60

Ser Ile His Asn Glu Glu Glu Asn Ala Phe Ile Leu Asp Thr Leu Lys
65 70 75 80

Lys Gln Trp Lys Gly Pro Asp Asp Ile Leu Leu Gly Met Phe Tyr Asp

85 90 95

Thr Asp Asp Ala Ser Phe Lys Trp Phe Asp Asn Ser Asn Met Thr Phe
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Asp Lys Trp Thr Asp Gln Asp Asp Asp Glu Asp Leu Val Asp Thr Cys
115 120 125

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Val Ser Ser Val Glu Gly Thr Leu Cys Lys Thr Ala Ile Pro Tyr Lys
145 150 155 160

Arg Lys Tyr Leu Ser Asp Asn His Ile Leu Ile Ser Ala Leu Val Ile
165 170 175

Ala Ser Thr Val Ile Leu Thr Val Leu Gly Ala Ile Ile Trp Phe Leu
180 185 190

Tyr Lys Lys His Ser Asp Ser Arg Phe Thr Thr Val Phe Ser Thr Ala
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Asn Glu Tyr Pro Val Gln Phe Asp
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gtc atg ccc cac gca gcg ctg tcc tcg ctc gtg ctg ctg agc ctc gcc 408
Met Pro His Ala Ala Leu Ser Ser Leu Val Leu Leu Ser Leu Ala
1 5 10 15

act gcc atc gtc gcc gac tgt cct tca tct acc tgg gtc cag ttc caa 456
Thr Ala Ile Val Ala Asp Cys Pro Ser Ser Thr Trp Val Gln Phe Gln
20 25 30

ggc agc tgt tat gct ttt ctt caa gta acc atc aat gtg gaa aac ata 504
Gly Ser Cys Tyr Ala Phe Leu Gln Val Thr Ile Asn Val Glu Asn Ile
35 40 45

gag gat gtc aga aaa cag tgc act gac cac ggg gca gac atg gta agc 552
Glu Asp Val Arg Lys Gln Cys Thr Asp His Gly Ala Asp Met Val Ser
50 55 60

ata cac aat gaa gag gaa aac gcg ttt ata ctg gac act ttg caa aag 600
Ile His Asn Glu Glu Glu Asn Ala Phe Ile Leu Asp Thr Leu Gln Lys
65 70 75

cga tgg aag ggt cca gat gat ctc ctg cta ggc atg ttc tat gac act 648
Arg Trp Lys Gly Pro Asp Asp Leu Leu Leu Gly Met Phe Tyr Asp Thr
80 85 90 95

gat gat gca act ttc aag tgg tat gat cat tca aat atg aca ttc gac 696
Asp Asp Ala Thr Phe Lys Trp Tyr Asp His Ser Asn Met Thr Phe Asp
100 105 110

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Lys Trp Ala Asp Gln Asp Gly Glu Asp Leu Val Asp Thr Cys Gly Phe
115 120 125

ctg tac acc aag aca ggt gaa tgg aga aaa ggg gat tgt gaa atc tct 792
Leu Tyr Thr Lys Thr Gly Glu Trp Arg Lys Gly Asp Cys Glu Ile Ser
130 135 140

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Ser Val Glu Gly Thr Leu Cys Lys Ala Ala Ile Pro Tyr Asp Lys Lys
145 150 155

tat tta tca gat aac cac att tta ata tcg act ctg gtg atc gct agc 888
Tyr Leu Ser Asp Asn His Ile Leu Ile Ser Thr Leu Val Ile Ala Ser
160 165 170 175

aca gta act ctg gca gtt ttg gga gcg atc att tgg ttc ctc tat aga 936
Thr Val Thr Leu Ala Val Leu Gly Ala Ile Ile Trp Phe Leu Tyr Arg
180 185 190

aga aac gcg cgc tct ggc ttc acc tct ttt tca cct gca cca ctg tca 984
Arg Asn Ala Arg Ser Gly Phe Thr Ser Phe Ser Pro Ala Pro Leu Ser
195 200 205

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Pro Tyr Ser Asp Gly Cys Ala Leu Val Val Ala Glu Glu Asp Glu Tyr
210 215 220

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35 40 45

Asp Val Arg Lys Gln Cys Thr Asp His Gly Ala Asp Met Val Ser Ile
50 55 60

His Asn Glu Glu Glu Asn Ala Phe Ile Leu Asp Thr Leu Gln Lys Arg
65 70 75 80

Trp Lys Gly Pro Asp Asp Leu Leu Leu Gly Met Phe Tyr Asp Thr Asp
85 90 95

Asp Ala Thr Phe Lys Trp Tyr Asp His Ser Asn Met Thr Phe Asp Lys
100 105 110

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115 120 125

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130 135 140

Val Glu Gly Thr Leu Cys Lys Ala Ala Ile Pro Tyr Asp Lys Lys Tyr
145 150 155 160

Leu Ser Asp Asn His Ile Leu Ile Ser Thr Leu Val Ile Ala Ser Thr
165 170 175

Val Thr Leu Ala Val Leu Gly Ala Ile Ile Trp Phe Leu Tyr Arg Arg
180 185 190

Asn Ala Arg Ser Gly Phe Thr Ser Phe Ser Pro Ala Pro Leu Ser Pro
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Val Gln Leu Asp
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His Glu Ala Ser Xaa Val Leu Leu Ser Leu Ala Thr Xaa Ile Phe Ala
1               5                  10                  15

gac tgt cct tcg tcc atc tgg gtt cag ttc caa ggc agc tgt tac act      96
Asp Cys Pro Ser Ser Ile Trp Val Gln Phe Gln Gly Ser Cys Tyr Thr
            20                  25                  30

ttt ctt caa gta acc atc aat gtg gaa aac ata gag gat gtc aga aag     144
Phe Leu Gln Val Thr Ile Asn Val Glu Asn Ile Glu Asp Val Arg Lys
        35                  40                  45

cag tgt act gat cac ggg gca gac ctg gta agt ata cac aat gaa gaa     192
Gln Cys Thr Asp His Gly Ala Asp Leu Val Ser Ile His Asn Glu Glu
    50                  55                  60

gaa aac gca ttt ata ctg gac act tta caa aag cga tgg aaa ggc ccg     240
Glu Asn Ala Phe Ile Leu Asp Thr Leu Gln Lys Arg Trp Lys Gly Pro
65                  70                  75                  80

gat gat ctt ctg cta ggc atg ttt tat gac act gat gat gca agt ttc     288
Asp Asp Leu Leu Leu Gly Met Phe Tyr Asp Thr Asp Asp Ala Ser Phe
                85                  90                  95

aag tgg ttt gat cag tca aat atg aca ttc gac aag tgg gca gat gag     336
```

Lys Trp Phe Asp Gln Ser Asn Met Thr Phe Asp Lys Trp Ala Asp Glu
100 105 110

gat ggt gag gac cta gtt gac acc tgt ggt ttt ctg tat gcc aag aca 384
Asp Gly Glu Asp Leu Val Asp Thr Cys Gly Phe Leu Tyr Ala Lys Thr
115 120 125

ggt gaa tgg aga aaa gga aat tgt gaa atg tct tct gtg acr gga aca 432
Gly Glu Trp Arg Lys Gly Asn Cys Glu Met Ser Ser Val Xaa Gly Thr
130 135 140

ctt tgc aaa aca gca atc cca tat gac aag aag tat tta tca gat aac 480
Leu Cys Lys Thr Ala Ile Pro Tyr Asp Lys Lys Tyr Leu Ser Asp Asn
145 150 155 160

cac att tta ata tcg act ctg gtg atc gct agc aca gtg act ctg gca 528
His Ile Leu Ile Ser Thr Leu Val Ile Ala Ser Thr Val Thr Leu Ala
165 170 175

gtt ttg gga gcg gtc att tgg ttc ctc tat aga agg agc gca cgc tct 576
Val Leu Gly Ala Val Ile Trp Phe Leu Tyr Arg Arg Ser Ala Arg Ser
180 185 190

ggc ttc acc tct ttc tct cct gca cca caa tca cct tac agt gat ggc 624
Gly Phe Thr Ser Phe Ser Pro Ala Pro Gln Ser Pro Tyr Ser Asp Gly
195 200 205

tgt gct ctg gta gtt gcg gaa gaa gat gaa tac tct gtt cag ctg gac 672
Cys Ala Leu Val Val Ala Glu Glu Asp Glu Tyr Ser Val Gln Leu Asp
210 215 220

tgagagtttg ggaacatcag acgagcacac tgaacacctt gacaagaaat aatttcctat 732

gcaagattgt catgtaaaat ttgccacgga aaactgaacc ttttatggta ttccttattc 792

ttctaacaat attttcatgt attcaatgtg acaaaacata aaccttctga ttaaaaggaa 852

aaaaagtagg tttcagaaaa ggaactagca cagagctaac ttacaggttt tcttaagtag 912

ttttcatttg agtaaatgaa agctacagta caataaagct ggtaaaacgc aaaaaaaaaa 972

aaaaaaa 979

<210> 11
<211> 224
<212> PRT
<213> mammalian

<220>
<221> misc_feature
<222> (5)..(5)
<223> The 'Xaa' at location 5 stands for Leu.

<220>
<221> misc_feature
<222> (13)..(13)
<223> The 'Xaa' at location 13 stands for Ala, Val, Asp or Gly.

<220>
<221> misc_feature
<222> (142)..(142)
<223> The 'Xaa' at location 142 stands for Thr.

<400> 11

His Glu Ala Ser Xaa Val Leu Leu Ser Leu Ala Thr Xaa Ile Phe Ala
1 5 10 15

Asp Cys Pro Ser Ser Ile Trp Val Gln Phe Gln Gly Ser Cys Tyr Thr
20 25 30

Phe Leu Gln Val Thr Ile Asn Val Glu Asn Ile Glu Asp Val Arg Lys
35 40 45

Gln Cys Thr Asp His Gly Ala Asp Leu Val Ser Ile His Asn Glu Glu
50 55 60

Glu Asn Ala Phe Ile Leu Asp Thr Leu Gln Lys Arg Trp Lys Gly Pro
65 70 75 80

Asp Asp Leu Leu Leu Gly Met Phe Tyr Asp Thr Asp Asp Ala Ser Phe
85 90 95

Lys Trp Phe Asp Gln Ser Asn Met Thr Phe Asp Lys Trp Ala Asp Glu
100 105 110

Asp Gly Glu Asp Leu Val Asp Thr Cys Gly Phe Leu Tyr Ala Lys Thr
115 120 125

Gly Glu Trp Arg Lys Gly Asn Cys Glu Met Ser Ser Val Xaa Gly Thr
130 135 140

Leu Cys Lys Thr Ala Ile Pro Tyr Asp Lys Lys Tyr Leu Ser Asp Asn
145 150 155 160

His Ile Leu Ile Ser Thr Leu Val Ile Ala Ser Thr Val Thr Leu Ala
165 170 175

Val Leu Gly Ala Val Ile Trp Phe Leu Tyr Arg Arg Ser Ala Arg Ser
180 185 190

Gly Phe Thr Ser Phe Ser Pro Ala Pro Gln Ser Pro Tyr Ser Asp Gly
195 200 205

Cys Ala Leu Val Val Ala Glu Glu Asp Glu Tyr Ser Val Gln Leu Asp
210 215 220

<210> 12
<211> 979
<212> DNA
<213> mammalian

<220>
<221> misc_feature
<223> Complementary DNA strand displayed in the 3' to 5' direction

<400> 12
gtgctccgga gcgascacga cgactcggat cggtgacrgt agaagcgact gacaggaagc 60

aggtagaccc aagtcaaggt tccgtcgaca atgtgaaaag aagttcattg gtagttacac 120

cttttgtatc tcctacagtc tttcgtcaca tgactagtgc cccgtctgga ccattcatat 180

gtgttacttc ttcttttgcg taaatatgac ctgtgaaatg ttttcgctac ctttccgggc 240

ctactagaag acgatccgta caaaatactg tgactactac gttcaaagtt caccaaacta 300

gtcagtttat actgtaagct gttcacccgt ctactcctac cactcctgga tcaactgtgg 360

acaccaaaag acatacggtt ctgtccactt acctcttttc ctttaacact ttacagaaga 420

cactgycctt gtgaaacgtt ttgtcgttag ggtatactgt tcttcataaa tagtctattg 480

gtgtaaaatt atagctgaga ccactagcga tcgtgtcact gagaccgtca aaaccctcgc 540

cagtaaacca aggagatatc ttcctcgcgt gcgagaccga agtggagaaa gagaggacgt 600

ggtgttagtg gaatgtcact accgacacga gaccatcaac gccttcttct acttatgaga 660

caagtcgacc tgactctcaa acccttgtag tctgctcgtg tgacttgtgg aactgttctt 720

tattaaagga tacgttctaa cagtacattt taaacggtgc cttttgactt ggaaaatacc 780

ataaggaata agaagattgt tataaaagta cataagttac actgttttgt atttggaaga 840

ctaattttcc ttttttttcat ccaaagtctt ttccttgatc gtgtctcgat tgaatgtcca 900

aaagaattca tcaaaagtaa actcatttac tttcgatgtc atgttatttc gaccattttg 960

cgtttttttt ttttttttt 979

<210> 13
<211> 483
<212> DNA
<213> mammalian

<220>
<221> misc_feature
<222> (43)..(43)
<223> "n" is an unknown nucleotide

<400> 13
gagctagttg acacctgtgc ctttttgcac accaagacag gtngattgga aaaaaggaaa 60

ctgtgaagtt tcttctgtgg aaggaaccct ttgtaaagca gctatcccat atgaaaagaa 120

atatttatca gataaccgca ttttaatatc agctttggtg attgctagca cagtaattct 180

gacagttctg ggagcagttg tttggttctt gtacaaaaga agtttggatt ctggtttcac 240

cacagttttt tcagctgcac accaatcacc ttataatgat gactgtgttt tagtagttgc 300

agaggaaaac gaatatgata ttcaatttaa ctaagatttt ggaaatatca gactaagaca 360

aataccttc agtgattcct ctgtaagatt tcaatataaa acctgataat gaaaattagt 420

ttttatgata tattacctta ttccagtaac attcattact cttatgtaaa atcactgatc 480

atg 483

<210> 14
<211> 27
<212> DNA
<213> mammalian

<220>
<221> CDS
<222> (1)..(27)
<223>

<400> 14
aaa gtg cct ctg ggc cct gat tac aca 27
Lys Val Pro Leu Gly Pro Asp Tyr Thr
1 5

<210> 15
<211> 9
<212> PRT
<213> mammalian

<400> 15

Lys Val Pro Leu Gly Pro Asp Tyr Thr
1 5

<210> 16

<211> 42
<212> DNA
<213> mammalian

<220>
<221> CDS
<222> (1)..(42)
<223>

<400> 16
aaa gtg cct ctg gac tgt cct tca tct act tgg att cag ttc 42
Lys Val Pro Leu Asp Cys Pro Ser Ser Thr Trp Ile Gln Phe
1 5 10

<210> 17
<211> 14
<212> PRT
<213> mammalian

<400> 17

Lys Val Pro Leu Asp Cys Pro Ser Ser Thr Trp Ile Gln Phe
1 5 10

<210> 18
<211> 42
<212> DNA
<213> mammalian

<220>
<221> CDS
<222> (1)..(42)
<223>

<400> 18
gct gcc gtc gcg gac tgt cct tca tct act tgg att cag ttc 42
Ala Ala Val Ala Asp Cys Pro Ser Ser Thr Trp Ile Gln Phe
1 5 10

<210> 19
<211> 14
<212> PRT
<213> mammalian

<400> 19

Ala Ala Val Ala Asp Cys Pro Ser Ser Thr Trp Ile Gln Phe
1 5 10

<210> 20
<211> 5454
<212> DNA
<213> mammalian

<220>
<221> CDS
<222> (1)..(5451)
<223>

<400> 20
atg agg aca ggc tgg gcg acc cct cgc cgc ccg gcg ggg ctc ctc atg 48
Met Arg Thr Gly Trp Ala Thr Pro Arg Arg Pro Ala Gly Leu Leu Met
1 5 10 15

ctg ctc ttc tgg ttc ttc gat ctc gcg gag ccc tct ggc cgc gca gct 96
Leu Leu Phe Trp Phe Phe Asp Leu Ala Glu Pro Ser Gly Arg Ala Ala
20 25 30

aat gac ccc ttc acc atc gtc cat gga aat acg ggc aag tgc atc aag 144

Asn Asp Pro Phe Thr Ile Val His Gly Asn Thr Gly Lys Cys Ile Lys
35 40 45

cca gtg tat ggc tgg ata gta gca gac gac tgt gat gaa act gag gac 192
Pro Val Tyr Gly Trp Ile Val Ala Asp Asp Cys Asp Glu Thr Glu Asp
50 55 60

aag tta tgg aag tgg gtg tcc cag cat cgg ctc ttt cat ttg cac tcc 240
Lys Leu Trp Lys Trp Val Ser Gln His Arg Leu Phe His Leu His Ser
65 70 75 80

caa aag tgc ctt ggc ctc gat att acc aaa tcg gta aat gag ctg aga 288
Gln Lys Cys Leu Gly Leu Asp Ile Thr Lys Ser Val Asn Glu Leu Arg
85 90 95

atg ttc agc tgt gac tcc agt gcc atg ctg tgg tgg aaa tgt gag cac 336
Met Phe Ser Cys Asp Ser Ser Ala Met Leu Trp Trp Lys Cys Glu His
100 105 110

cac tct ctg tac gga gct gcc cgg tac cgg ctg gct ctg aag gat gga 384
His Ser Leu Tyr Gly Ala Ala Arg Tyr Arg Leu Ala Leu Lys Asp Gly
115 120 125

cat ggc aca gca atc tca aat gca tct gat gtc tgg aag aaa gga ggc 432
His Gly Thr Ala Ile Ser Asn Ala Ser Asp Val Trp Lys Lys Gly Gly
130 135 140

tca gag gaa agc ctt tgt gac cag cct tat cat gag atc tat acc aga 480
Ser Glu Glu Ser Leu Cys Asp Gln Pro Tyr His Glu Ile Tyr Thr Arg
145 150 155 160

gat ggg aac tct tat ggg aga cct tgt gaa ttt cca ttc tta att gat 528
Asp Gly Asn Ser Tyr Gly Arg Pro Cys Glu Phe Pro Phe Leu Ile Asp
165 170 175

ggg acc tgg cat cat gat tgc att ctt gat gaa gat cat agt ggg cca 576
Gly Thr Trp His His Asp Cys Ile Leu Asp Glu Asp His Ser Gly Pro
180 185 190

tgg tgt gcc acc acc tta aat tat gaa tat gac cga aag tgg ggc atc 624
Trp Cys Ala Thr Thr Leu Asn Tyr Glu Tyr Asp Arg Lys Trp Gly Ile
195 200 205

tgc tta aag cct gaa aac ggt tgt gaa gat aat tgg gaa aag aac gag 672
Cys Leu Lys Pro Glu Asn Gly Cys Glu Asp Asn Trp Glu Lys Asn Glu
210 215 220

cag ttt gga agt tgc tac caa ttt aat act cag acg gct ctt tct tgg 720
Gln Phe Gly Ser Cys Tyr Gln Phe Asn Thr Gln Thr Ala Leu Ser Trp
225 230 235 240

aaa gaa gct tat gtt tca tgt cag aat caa gga gct gat tta ctg agc 768
Lys Glu Ala Tyr Val Ser Cys Gln Asn Gln Gly Ala Asp Leu Leu Ser
245 250 255

atc aac agt gct gct gaa tta act tac ctt aaa gaa aaa gaa ggc att 816
Ile Asn Ser Ala Ala Glu Leu Thr Tyr Leu Lys Glu Lys Glu Gly Ile
260 265 270

gct aag att ttc tgg att ggt tta aat cag cta tac tct gct aga ggc 864
Ala Lys Ile Phe Trp Ile Gly Leu Asn Gln Leu Tyr Ser Ala Arg Gly
275 280 285

tgg gaa tgg tca gac cac aaa cca tta aac ttt ctc aac tgg gat cca 912
Trp Glu Trp Ser Asp His Lys Pro Leu Asn Phe Leu Asn Trp Asp Pro
290 295 300

gac agg ccc agt gca cct act ata ggt ggc tcc agc tgt gca aga atg 960
Asp Arg Pro Ser Ala Pro Thr Ile Gly Gly Ser Ser Cys Ala Arg Met
305 310 315 320

gat gct gag tct ggt ctg tgg cag agc ttt tcc tgt gaa gct caa ctg 1008
Asp Ala Glu Ser Gly Leu Trp Gln Ser Phe Ser Cys Glu Ala Gln Leu
325 330 335

ccc tat gtc tgc agg aaa cca tta aat aat aca gtg gag tta aca gat 1056

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Pro Tyr Val Cys Arg Lys Pro Leu Asn Asn Thr Val Glu Leu Thr Asp
            340                 345                 350

gtc tgg aca tac tca gat acc cgc tgt gat gca ggc tgg ctg cca aat   1104
Val Trp Thr Tyr Ser Asp Thr Arg Cys Asp Ala Gly Trp Leu Pro Asn
        355                 360                 365

aat gga ttt tgc tat ctg ctg gta aat gaa agt aat tcc tgg gat aag   1152
Asn Gly Phe Cys Tyr Leu Leu Val Asn Glu Ser Asn Ser Trp Asp Lys
    370                 375                 380

gca cat gcg aaa tgc aaa gcc ttc agt agt gac cta atc agc att cat   1200
Ala His Ala Lys Cys Lys Ala Phe Ser Ser Asp Leu Ile Ser Ile His
385                 390                 395                 400

tct cta gca gat gtg gag gtg gtt gtc aca aaa ctc cat aat gag gat   1248
Ser Leu Ala Asp Val Glu Val Val Val Thr Lys Leu His Asn Glu Asp
                405                 410                 415

atc aaa gaa gaa gtg tgg ata ggc ctt aag aac ata aac ata cca act   1296
Ile Lys Glu Glu Val Trp Ile Gly Leu Lys Asn Ile Asn Ile Pro Thr
            420                 425                 430

tta ttt cag tgg tca gat ggt act gaa gtt act cta aca tat tgg gat   1344
Leu Phe Gln Trp Ser Asp Gly Thr Glu Val Thr Leu Thr Tyr Trp Asp
        435                 440                 445

gag aat gag cca aat gtt ccc tac aat aag acg ccc aac tgt gtt tcc   1392
Glu Asn Glu Pro Asn Val Pro Tyr Asn Lys Thr Pro Asn Cys Val Ser
    450                 455                 460

tac tta gga gag cta ggt cag tgg aaa gtc caa tca tgt gag gag aaa   1440
Tyr Leu Gly Glu Leu Gly Gln Trp Lys Val Gln Ser Cys Glu Glu Lys
465                 470                 475                 480

cta aaa tat gta tgc aag aga aag gga gaa aaa ctg aat gac gca agt   1488
Leu Lys Tyr Val Cys Lys Arg Lys Gly Glu Lys Leu Asn Asp Ala Ser
                485                 490                 495
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tct gat aag atg tgt cct cca gat gag ggc tgg aag aga cat gga gaa     1536
Ser Asp Lys Met Cys Pro Pro Asp Glu Gly Trp Lys Arg His Gly Glu
            500                 505                 510

acc tgt tac aag att tat gag gat gag gtc cct ttt gga aca aac tgc     1584
Thr Cys Tyr Lys Ile Tyr Glu Asp Glu Val Pro Phe Gly Thr Asn Cys
        515                 520                 525

aat ctg act atc act agc aga ttt gag caa gaa tac cta aat gat ttg     1632
Asn Leu Thr Ile Thr Ser Arg Phe Glu Gln Glu Tyr Leu Asn Asp Leu
    530                 535                 540

atg aaa aag tat gat aaa tct cta aga aaa tac ttc tgg act ggc ctg     1680
Met Lys Lys Tyr Asp Lys Ser Leu Arg Lys Tyr Phe Trp Thr Gly Leu
545                 550                 555                 560

aga gat gta gat tct tgt gga gag tat aac tgg gca act gtt ggt gga     1728
Arg Asp Val Asp Ser Cys Gly Glu Tyr Asn Trp Ala Thr Val Gly Gly
                565                 570                 575

aga agg cgg gct gta acc ttt tcc aac tgg aat ttt ctt gag cca gct     1776
Arg Arg Arg Ala Val Thr Phe Ser Asn Trp Asn Phe Leu Glu Pro Ala
            580                 585                 590

tcc ccg ggc ggc tgc gtg gct atg tct act gga aag tct gtt gga aag     1824
Ser Pro Gly Gly Cys Val Ala Met Ser Thr Gly Lys Ser Val Gly Lys
        595                 600                 605

tgg gag gtg aag gac tgc aga agc ttc aaa gca ctt tca att tgc aag     1872
Trp Glu Val Lys Asp Cys Arg Ser Phe Lys Ala Leu Ser Ile Cys Lys
    610                 615                 620

aaa atg agt gga ccc ctt ggg cct gaa gaa gca tcc cct aag cct gat     1920
Lys Met Ser Gly Pro Leu Gly Pro Glu Glu Ala Ser Pro Lys Pro Asp
625                 630                 635                 640

gac ccc tgt cct gaa ggc tgg cag agt ttc ccc gca agt ctt tct tgt     1968
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Asp Pro Cys Pro Glu Gly Trp Gln Ser Phe Pro Ala Ser Leu Ser Cys
645 650 655

tat aag gta ttc cat gca gaa aga att gta aga aag agg aac tgg gaa 2016
Tyr Lys Val Phe His Ala Glu Arg Ile Val Arg Lys Arg Asn Trp Glu
660 665 670

gaa gct gaa cga ttc tgc caa gcc ctt gga gca cac ctt tct agc ttc 2064
Glu Ala Glu Arg Phe Cys Gln Ala Leu Gly Ala His Leu Ser Ser Phe
675 680 685

agc cat gtg gat gaa ata aag gaa ttt ctt cac ttt tta acg gac cag 2112
Ser His Val Asp Glu Ile Lys Glu Phe Leu His Phe Leu Thr Asp Gln
690 695 700

ttc agt ggc cag cat tgg ctg tgg att ggt ttg aat aaa agg agc cca 2160
Phe Ser Gly Gln His Trp Leu Trp Ile Gly Leu Asn Lys Arg Ser Pro
705 710 715 720

gat tta caa gga tcc tgg caa tgg agt gat cgt aca cca gtg tct act 2208
Asp Leu Gln Gly Ser Trp Gln Trp Ser Asp Arg Thr Pro Val Ser Thr
725 730 735

att atc atg cca aat gag ttt cag cag gat tat gac atc aga gac tgt 2256
Ile Ile Met Pro Asn Glu Phe Gln Gln Asp Tyr Asp Ile Arg Asp Cys
740 745 750

gct gct gtc aag gta ttt cat agg cca tgg cga aga ggc tgg cat ttc 2304
Ala Ala Val Lys Val Phe His Arg Pro Trp Arg Arg Gly Trp His Phe
755 760 765

tat gat gat aga gaa ttt att tat ttg agg cct ttt gct tgt gat aca 2352
Tyr Asp Asp Arg Glu Phe Ile Tyr Leu Arg Pro Phe Ala Cys Asp Thr
770 775 780

aaa ctt gaa tgg gtg tgc caa att cca aaa ggc cgt act cca aaa aca 2400
Lys Leu Glu Trp Val Cys Gln Ile Pro Lys Gly Arg Thr Pro Lys Thr
785 790 795 800

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cca gac tgg tac aat cca gac cgt gct gga att cat gga cct cca ctt      2448
Pro Asp Trp Tyr Asn Pro Asp Arg Ala Gly Ile His Gly Pro Pro Leu
                805                 810                 815

ata att gaa gga agt gaa tat tgg ttt gtt gct gat ctt cac cta aac      2496
Ile Ile Glu Gly Ser Glu Tyr Trp Phe Val Ala Asp Leu His Leu Asn
            820                 825                 830

tat gaa gaa gcc gtc ctg tac tgt gcc agc aat cac agc ttt ctt gcg      2544
Tyr Glu Glu Ala Val Leu Tyr Cys Ala Ser Asn His Ser Phe Leu Ala
        835                 840                 845

act ata aca tct ttt gtg gga cta aaa gcc atc aaa aac aaa ata gca      2592
Thr Ile Thr Ser Phe Val Gly Leu Lys Ala Ile Lys Asn Lys Ile Ala
    850                 855                 860

aat ata tct ggt gat gga cag aag tgg tgg ata aga att agc gag tgg      2640
Asn Ile Ser Gly Asp Gly Gln Lys Trp Trp Ile Arg Ile Ser Glu Trp
865                 870                 875                 880

cca ata gat gat cat ttt aca tac tca cga tat cca tgg cac cgc ttt      2688
Pro Ile Asp Asp His Phe Thr Tyr Ser Arg Tyr Pro Trp His Arg Phe
                885                 890                 895

cct gtg aca ttt gga gag gaa tgc ttg tac atg tct gcc aag act tgg      2736
Pro Val Thr Phe Gly Glu Glu Cys Leu Tyr Met Ser Ala Lys Thr Trp
            900                 905                 910

ctt atc gac tta ggt aaa cca aca gac tgt agt acc aag ttg ccc ttc      2784
Leu Ile Asp Leu Gly Lys Pro Thr Asp Cys Ser Thr Lys Leu Pro Phe
        915                 920                 925

atc tgt gaa aaa tat aat gtt tct tcg tta gag aaa tac agc cca gat      2832
Ile Cys Glu Lys Tyr Asn Val Ser Ser Leu Glu Lys Tyr Ser Pro Asp
    930                 935                 940

tct gca gct aaa gtg caa tgt tct gag caa tgg att cct ttt cag aat      2880
```

```
Ser Ala Ala Lys Val Gln Cys Ser Glu Gln Trp Ile Pro Phe Gln Asn
945                 950                 955                 960

aag tgt ttt cta aag atc aaa ccc gtg tct ctc aca ttt tct caa gca      2928
Lys Cys Phe Leu Lys Ile Lys Pro Val Ser Leu Thr Phe Ser Gln Ala
                965                 970                 975

agc gat acc tgt cac tcc tat ggt ggc acc ctt cct tca gtg ttg agc      2976
Ser Asp Thr Cys His Ser Tyr Gly Gly Thr Leu Pro Ser Val Leu Ser
            980                 985                 990

cag att gaa caa gac ttt att aca tcc ttg ctt ccg gat atg gaa gct      3024
Gln Ile Glu Gln Asp Phe Ile Thr Ser Leu Leu Pro Asp Met Glu Ala
        995                 1000                1005

act tta tgg att ggt ttg cgc tgg act gcc tat gaa aag ata aac          3069
Thr Leu Trp Ile Gly Leu Arg Trp Thr Ala Tyr Glu Lys Ile Asn
    1010                1015                1020

aaa tgg aca gat aac aga gag ctg acg tac agt aac ttt cac cca          3114
Lys Trp Thr Asp Asn Arg Glu Leu Thr Tyr Ser Asn Phe His Pro
    1025                1030                1035

tta ttg gtt agt ggg agg ctg aga ata cca gaa aat ttt ttt gag          3159
Leu Leu Val Ser Gly Arg Leu Arg Ile Pro Glu Asn Phe Phe Glu
    1040                1045                1050

gaa gag tct cgc tac cac tgt gcc cta ata ctc aac ctc caa aaa          3204
Glu Glu Ser Arg Tyr His Cys Ala Leu Ile Leu Asn Leu Gln Lys
    1055                1060                1065

tca ccg ttt act ggg acg tgg aat ttt aca tcc tgc agt gaa cgc          3249
Ser Pro Phe Thr Gly Thr Trp Asn Phe Thr Ser Cys Ser Glu Arg
    1070                1075                1080

cac ttt gtg tct ctc tgt cag aaa tat tca gaa gtt aaa agc aga          3294
His Phe Val Ser Leu Cys Gln Lys Tyr Ser Glu Val Lys Ser Arg
    1085                1090                1095
```

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cag acg  ttg cag aat gct tca  gaa act gta aag tat  cta aat aat      3339
Gln Thr  Leu Gln Asn Ala Ser  Glu Thr Val Lys Tyr  Leu Asn Asn
    1100                 1105                 1110

ctg tac  aaa ata atc cca aag  act ctg act tgg cac  agt gct aaa      3384
Leu Tyr  Lys Ile Ile Pro Lys  Thr Leu Thr Trp His  Ser Ala Lys
    1115                 1120                 1125

agg gag  tgt ctg aaa agt aac  atg cag ctg gtg agc  atc acg gac      3429
Arg Glu  Cys Leu Lys Ser Asn  Met Gln Leu Val Ser  Ile Thr Asp
    1130                 1135                 1140

cct tac  cag cag gca ttc ctc  agt gtg cag gcg ctc  ctt cac aac      3474
Pro Tyr  Gln Gln Ala Phe Leu  Ser Val Gln Ala Leu  Leu His Asn
    1145                 1150                 1155

tct tcc  tta tgg atc gga ctc  ttc agt caa gat gat  gaa ctc aac      3519
Ser Ser  Leu Trp Ile Gly Leu  Phe Ser Gln Asp Asp  Glu Leu Asn
    1160                 1165                 1170

ttt ggt  tgg tca gat ggg aaa  cgt ctt cat ttt agt  cgc tgg gct      3564
Phe Gly  Trp Ser Asp Gly Lys  Arg Leu His Phe Ser  Arg Trp Ala
    1175                 1180                 1185

gaa act  aat ggg caa ctc gaa  gac tgt gta gta tta  gac act gat      3609
Glu Thr  Asn Gly Gln Leu Glu  Asp Cys Val Val Leu  Asp Thr Asp
    1190                 1195                 1200

gga ttc  tgg aaa aca gtt gat  tgc aat gac aat caa  cca ggt gct      3654
Gly Phe  Trp Lys Thr Val Asp  Cys Asn Asp Asn Gln  Pro Gly Ala
    1205                 1210                 1215

att tgc  tac tat tca gga aat  gag act gaa aaa gag  gtc aaa cca      3699
Ile Cys  Tyr Tyr Ser Gly Asn  Glu Thr Glu Lys Glu  Val Lys Pro
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gtt gac  agt gtt aaa tgt cca  tct cct gtt cta aat  act ccg tgg      3744
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Val Asp  Ser Val Lys Cys Pro  Ser Pro Val Leu Asn  Thr Pro Trp
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ata cca  ttt cag aac tgt tgc  tac aat ttc ata ata  aca aag aat      3789
Ile Pro  Phe Gln Asn Cys Cys  Tyr Asn Phe Ile Ile  Thr Lys Asn
    1250                 1255                 1260

agg cat  atg gca aca aca cag  gat gaa gtt cat act  aaa tgc cag      3834
Arg His  Met Ala Thr Thr Gln  Asp Glu Val His Thr  Lys Cys Gln
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aaa ctg  aat cca aaa tca cat  att ctg agt att cga  gat gaa aag      3879
Lys Leu  Asn Pro Lys Ser His  Ile Leu Ser Ile Arg  Asp Glu Lys
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gag aat  aac ttt gtt ctt gag  caa ctg ctg tac ttc  aat tat atg      3924
Glu Asn  Asn Phe Val Leu Glu  Gln Leu Leu Tyr Phe  Asn Tyr Met
    1295                 1300                 1305

gct tca  tgg gtc atg tta gga  ata act tat aga aat  aat tct ctt      3969
Ala Ser  Trp Val Met Leu Gly  Ile Thr Tyr Arg Asn  Asn Ser Leu
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atg tgg  ttt gat aag acc cca  ctg tca tat aca cat  tgg aga gca      4014
Met Trp  Phe Asp Lys Thr Pro  Leu Ser Tyr Thr His  Trp Arg Ala
    1325                 1330                 1335

gga aga  cca act ata aaa aat  gag aag ttt ttg gct  ggt tta agt      4059
Gly Arg  Pro Thr Ile Lys Asn  Glu Lys Phe Leu Ala  Gly Leu Ser
    1340                 1345                 1350

act gac  ggc ttc tgg gat att  caa acc ttt aaa gtt  att gaa gaa      4104
Thr Asp  Gly Phe Trp Asp Ile  Gln Thr Phe Lys Val  Ile Glu Glu
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gca gtt  tat ttt cac cag cac  agc att ctt gct tgt  aaa att gaa      4149
Ala Val  Tyr Phe His Gln His  Ser Ile Leu Ala Cys  Lys Ile Glu
    1370                 1375                 1380
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Met Val Asp Tyr Lys Glu Glu His Asn Thr Thr Leu Pro Gln Phe
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atg cca tat gaa gat ggt att tac agt gtt att caa aaa aag gta 4239
Met Pro Tyr Glu Asp Gly Ile Tyr Ser Val Ile Gln Lys Lys Val
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aca tgg tat gaa gca tta aac atg tgt tct caa agt gga ggt cac 4284
Thr Trp Tyr Glu Ala Leu Asn Met Cys Ser Gln Ser Gly Gly His
1415 1420 1425

ttg gca agc gtt cac aac caa aat ggc cag ctc ttt ctg gaa gat 4329
Leu Ala Ser Val His Asn Gln Asn Gly Gln Leu Phe Leu Glu Asp
1430 1435 1440

att gta aaa cgt gat gga ttt cca cta tgg gtt ggg ctc tca agt 4374
Ile Val Lys Arg Asp Gly Phe Pro Leu Trp Val Gly Leu Ser Ser
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cat gat gga agt gaa tca agt ttt gaa tgg tct gat ggt agt aca 4419
His Asp Gly Ser Glu Ser Ser Phe Glu Trp Ser Asp Gly Ser Thr
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ttt gac tat atc cca tgg aaa ggc caa aca tct cct gga aat tgt 4464
Phe Asp Tyr Ile Pro Trp Lys Gly Gln Thr Ser Pro Gly Asn Cys
1475 1480 1485

gtt ctc ttg gat cca aaa gga act tgg aaa cat gaa aaa tgc aac 4509
Val Leu Leu Asp Pro Lys Gly Thr Trp Lys His Glu Lys Cys Asn
1490 1495 1500

tct gtt aag gat ggt gct att tgt tat aaa cct aca aaa tct aaa 4554
Ser Val Lys Asp Gly Ala Ile Cys Tyr Lys Pro Thr Lys Ser Lys
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Lys Leu  Ser Arg Leu Thr Tyr  Ser Ser Arg Cys Pro  Ala Ala Lys
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Glu Asn  Gly Ser Arg Trp Ile  Gln Tyr Lys Gly His  Cys Tyr Lys
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tct gat  cag gca ttg cac agt  ttt tca gag gcc aaa  aaa ttg tgt      4689
Ser Asp  Gln Ala Leu His Ser  Phe Ser Glu Ala Lys  Lys Leu Cys
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tca aaa  cat gat cac tct gca  act atc gtt tcc ata  aaa gat gaa      4734
Ser Lys  His Asp His Ser Ala  Thr Ile Val Ser Ile  Lys Asp Glu
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gat gag  aat aaa ttt gtg agc  aga ctg atg agg gaa  aat aat aac      4779
Asp Glu  Asn Lys Phe Val Ser  Arg Leu Met Arg Glu  Asn Asn Asn
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att acc  atg aga gtt tgg ctt  gga tta tct caa cat  tct gtt gac      4824
Ile Thr  Met Arg Val Trp Leu  Gly Leu Ser Gln His  Ser Val Asp
    1595                  1600                  1605

tgt cct  tca tct act tgg att  cag ttc caa gac agt  tgt tac att      4869
Cys Pro  Ser Ser Thr Trp Ile  Gln Phe Gln Asp Ser  Cys Tyr Ile
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Phe Leu  Gln Glu Ala Ile Lys  Val Glu Ser Ile Glu  Asp Val Arg
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aat cag  tgt act gac cat gga  gcg gac atg ata agc  ata cat aat      4959
Asn Gln  Cys Thr Asp His Gly  Ala Asp Met Ile Ser  Ile His Asn
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gaa gaa  gaa aat gct ttt ata  ctg gat act ttg aaa  aag caa tgg      5004
Glu Glu  Glu Asn Ala Phe Ile  Leu Asp Thr Leu Lys  Lys Gln Trp
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Lys Gly  Pro Asp Asp Ile Leu  Leu Gly Met Phe Tyr  Asp Thr Asp
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gat gcg  agt ttc aag tgg ttt  gat aat tca aat atg  aca ttt gat      5094
Asp Ala  Ser Phe Lys Trp Phe  Asp Asn Ser Asn Met  Thr Phe Asp
    1685                 1690                 1695

aag tgg  aca gac caa gat gat  gat gag gat tta gtt  gac acc tgt      5139
Lys Trp  Thr Asp Gln Asp Asp  Asp Glu Asp Leu Val  Asp Thr Cys
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gct ttt  ctg cac atc aag aca  ggt gaa tgg aaa aaa  gga aat tgt      5184
Ala Phe  Leu His Ile Lys Thr  Gly Glu Trp Lys Lys  Gly Asn Cys
    1715                 1720                 1725

gaa gtt  tct tct gtg gaa gga  aca cta tgc aaa aca  gct atc cca      5229
Glu Val  Ser Ser Val Glu Gly  Thr Leu Cys Lys Thr  Ala Ile Pro
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tac aaa  agg aaa tat tta tca  gat aac cac att tta  ata tca gca      5274
Tyr Lys  Arg Lys Tyr Leu Ser  Asp Asn His Ile Leu  Ile Ser Ala
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Leu Val  Ile Ala Ser Thr Val  Ile Leu Thr Val Leu  Gly Ala Ile
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att tgg  ttc ctg tac aaa aaa  cat tct gat tct cgt  ttc acc aca      5364
Ile Trp  Phe Leu Tyr Lys Lys  His Ser Asp Ser Arg  Phe Thr Thr
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gtt ttt  tca acc gca ccc caa  tca cct tat aat gaa  gac tgt gtt      5409
Val Phe  Ser Thr Ala Pro Gln  Ser Pro Tyr Asn Glu  Asp Cys Val
    1790                 1795                 1800

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Pro Val Tyr Gly Trp Ile Val Ala Asp Asp Cys Asp Glu Thr Glu Asp
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Lys Leu Trp Lys Trp Val Ser Gln His Arg Leu Phe His Leu His Ser
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Gln Lys Cys Leu Gly Leu Asp Ile Thr Lys Ser Val Asn Glu Leu Arg
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Met Phe Ser Cys Asp Ser Ser Ala Met Leu Trp Trp Lys Cys Glu His
100 105 110

His Ser Leu Tyr Gly Ala Ala Arg Tyr Arg Leu Ala Leu Lys Asp Gly
115 120 125

His Gly Thr Ala Ile Ser Asn Ala Ser Asp Val Trp Lys Lys Gly Gly
130 135 140

Ser Glu Glu Ser Leu Cys Asp Gln Pro Tyr His Glu Ile Tyr Thr Arg
145 150 155 160

Asp Gly Asn Ser Tyr Gly Arg Pro Cys Glu Phe Pro Phe Leu Ile Asp
165 170 175

Gly Thr Trp His His Asp Cys Ile Leu Asp Glu Asp His Ser Gly Pro
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Trp Cys Ala Thr Thr Leu Asn Tyr Glu Tyr Asp Arg Lys Trp Gly Ile
195 200 205

Cys Leu Lys Pro Glu Asn Gly Cys Glu Asp Asn Trp Glu Lys Asn Glu
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Gln Phe Gly Ser Cys Tyr Gln Phe Asn Thr Gln Thr Ala Leu Ser Trp
225 230 235 240

Lys Glu Ala Tyr Val Ser Cys Gln Asn Gln Gly Ala Asp Leu Leu Ser
245 250 255

Ile Asn Ser Ala Ala Glu Leu Thr Tyr Leu Lys Glu Lys Glu Gly Ile

260 265 270

Ala Lys Ile Phe Trp Ile Gly Leu Asn Gln Leu Tyr Ser Ala Arg Gly
275 280 285

Trp Glu Trp Ser Asp His Lys Pro Leu Asn Phe Leu Asn Trp Asp Pro
290 295 300

Asp Arg Pro Ser Ala Pro Thr Ile Gly Gly Ser Ser Cys Ala Arg Met
305 310 315 320

Asp Ala Glu Ser Gly Leu Trp Gln Ser Phe Ser Cys Glu Ala Gln Leu
325 330 335

Pro Tyr Val Cys Arg Lys Pro Leu Asn Asn Thr Val Glu Leu Thr Asp
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Val Trp Thr Tyr Ser Asp Thr Arg Cys Asp Ala Gly Trp Leu Pro Asn
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Asn Gly Phe Cys Tyr Leu Leu Val Asn Glu Ser Asn Ser Trp Asp Lys
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Ala His Ala Lys Cys Lys Ala Phe Ser Ser Asp Leu Ile Ser Ile His
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Ser Leu Ala Asp Val Glu Val Val Val Thr Lys Leu His Asn Glu Asp
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Ile Lys Glu Glu Val Trp Ile Gly Leu Lys Asn Ile Asn Ile Pro Thr
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Thr Cys Tyr Lys Ile Tyr Glu Asp Glu Val Pro Phe Gly Thr Asn Cys
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Ser Pro Gly Gly Cys Val Ala Met Ser Thr Gly Lys Ser Val Gly Lys
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Trp Glu Val Lys Asp Cys Arg Ser Phe Lys Ala Leu Ser Ile Cys Lys
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Asp Pro Cys Pro Glu Gly Trp Gln Ser Phe Pro Ala Ser Leu Ser Cys
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Tyr Lys Val Phe His Ala Glu Arg Ile Val Arg Lys Arg Asn Trp Glu
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Glu Ala Glu Arg Phe Cys Gln Ala Leu Gly Ala His Leu Ser Ser Phe
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Ser His Val Asp Glu Ile Lys Glu Phe Leu His Phe Leu Thr Asp Gln
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Phe Ser Gly Gln His Trp Leu Trp Ile Gly Leu Asn Lys Arg Ser Pro
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Asp Leu Gln Gly Ser Trp Gln Trp Ser Asp Arg Thr Pro Val Ser Thr
725 730 735

Ile Ile Met Pro Asn Glu Phe Gln Gln Asp Tyr Asp Ile Arg Asp Cys
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Ala Ala Val Lys Val Phe His Arg Pro Trp Arg Arg Gly Trp His Phe
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Tyr Asp Asp Arg Glu Phe Ile Tyr Leu Arg Pro Phe Ala Cys Asp Thr
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Lys Leu Glu Trp Val Cys Gln Ile Pro Lys Gly Arg Thr Pro Lys Thr
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Pro Asp Trp Tyr Asn Pro Asp Arg Ala Gly Ile His Gly Pro Pro Leu
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820 825 830

Tyr Glu Glu Ala Val Leu Tyr Cys Ala Ser Asn His Ser Phe Leu Ala
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Thr Ile Thr Ser Phe Val Gly Leu Lys Ala Ile Lys Asn Lys Ile Ala
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Asn Ile Ser Gly Asp Gly Gln Lys Trp Trp Ile Arg Ile Ser Glu Trp

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Pro Ile Asp Asp His Phe Thr Tyr Ser Arg Tyr Pro Trp His Arg Phe
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Pro Val Thr Phe Gly Glu Glu Cys Leu Tyr Met Ser Ala Lys Thr Trp
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Leu Ile Asp Leu Gly Lys Pro Thr Asp Cys Ser Thr Lys Leu Pro Phe
915 920 925

Ile Cys Glu Lys Tyr Asn Val Ser Ser Leu Glu Lys Tyr Ser Pro Asp
930 935 940

Ser Ala Ala Lys Val Gln Cys Ser Glu Gln Trp Ile Pro Phe Gln Asn
945 950 955 960

Lys Cys Phe Leu Lys Ile Lys Pro Val Ser Leu Thr Phe Ser Gln Ala
965 970 975

Ser Asp Thr Cys His Ser Tyr Gly Gly Thr Leu Pro Ser Val Leu Ser
980 985 990

Gln Ile Glu Gln Asp Phe Ile Thr Ser Leu Leu Pro Asp Met Glu Ala
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Thr Leu Trp Ile Gly Leu Arg Trp Thr Ala Tyr Glu Lys Ile Asn
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Lys Trp Thr Asp Asn Arg Glu Leu Thr Tyr Ser Asn Phe His Pro
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Glu Glu Ser Arg Tyr His Cys Ala Leu Ile Leu Asn Leu Gln Lys
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Ser Pro Phe Thr Gly Thr Trp Asn Phe Thr Ser Cys Ser Glu Arg
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His Phe Val Ser Leu Cys Gln Lys Tyr Ser Glu Val Lys Ser Arg
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Gln Thr Leu Gln Asn Ala Ser Glu Thr Val Lys Tyr Leu Asn Asn
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Leu Tyr Lys Ile Ile Pro Lys Thr Leu Thr Trp His Ser Ala Lys
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Arg Glu Cys Leu Lys Ser Asn Met Gln Leu Val Ser Ile Thr Asp
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Pro Tyr Gln Gln Ala Phe Leu Ser Val Gln Ala Leu Leu His Asn
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Ser Ser Leu Trp Ile Gly Leu Phe Ser Gln Asp Asp Glu Leu Asn

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Phe Gly Trp Ser Asp Gly Lys Arg Leu His Phe Ser Arg Trp Ala
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Glu Thr Asn Gly Gln Leu Glu Asp Cys Val Val Leu Asp Thr Asp
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Gly Phe Trp Lys Thr Val Asp Cys Asn Asp Asn Gln Pro Gly Ala
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Ile Cys Tyr Tyr Ser Gly Asn Glu Thr Glu Lys Glu Val Lys Pro
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Val Asp Ser Val Lys Cys Pro Ser Pro Val Leu Asn Thr Pro Trp
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Arg His Met Ala Thr Thr Gln Asp Glu Val His Thr Lys Cys Gln
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Met Trp Phe Asp Lys Thr Pro Leu Ser Tyr Thr His Trp Arg Ala
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Gly Arg Pro Thr Ile Lys Asn Glu Lys Phe Leu Ala Gly Leu Ser
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Thr Asp Gly Phe Trp Asp Ile Gln Thr Phe Lys Val Ile Glu Glu
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Met Val Asp Tyr Lys Glu Glu His Asn Thr Thr Leu Pro Gln Phe
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Leu Ala Ser Val His Asn Gln Asn Gly Gln Leu Phe Leu Glu Asp
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Ile Val Lys Arg Asp Gly Phe Pro Leu Trp Val Gly Leu Ser Ser

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His Asp Gly Ser Glu Ser Ser Phe Glu Trp Ser Asp Gly Ser Thr
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Phe Asp Tyr Ile Pro Trp Lys Gly Gln Thr Ser Pro Gly Asn Cys
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Val Leu Leu Asp Pro Lys Gly Thr Trp Lys His Glu Lys Cys Asn
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Ser Val Lys Asp Gly Ala Ile Cys Tyr Lys Pro Thr Lys Ser Lys
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Glu Asn Gly Ser Arg Trp Ile Gln Tyr Lys Gly His Cys Tyr Lys
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Ser Asp Gln Ala Leu His Ser Phe Ser Glu Ala Lys Lys Leu Cys
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Ser Lys His Asp His Ser Ala Thr Ile Val Ser Ile Lys Asp Glu
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Asp Glu Asn Lys Phe Val Ser Arg Leu Met Arg Glu Asn Asn Asn
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Ile Thr Met Arg Val Trp Leu Gly Leu Ser Gln His Ser Val Asp
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Cys Pro Ser Ser Thr Trp Ile Gln Phe Gln Asp Ser Cys Tyr Ile
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Tyr Lys Arg Lys Tyr Leu Ser Asp Asn His Ile Leu Ile Ser Ala
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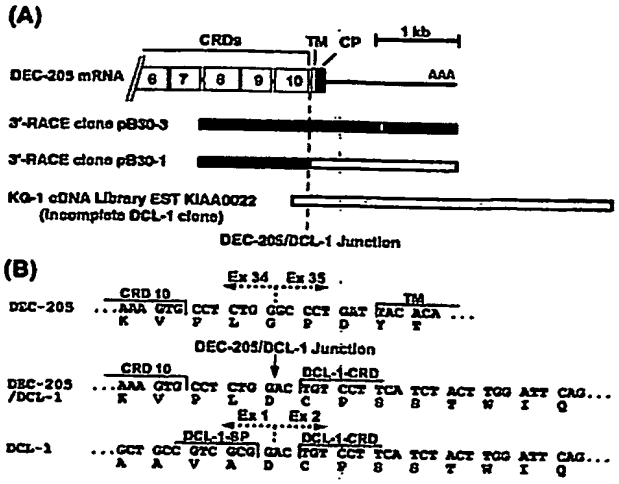


Figure 1

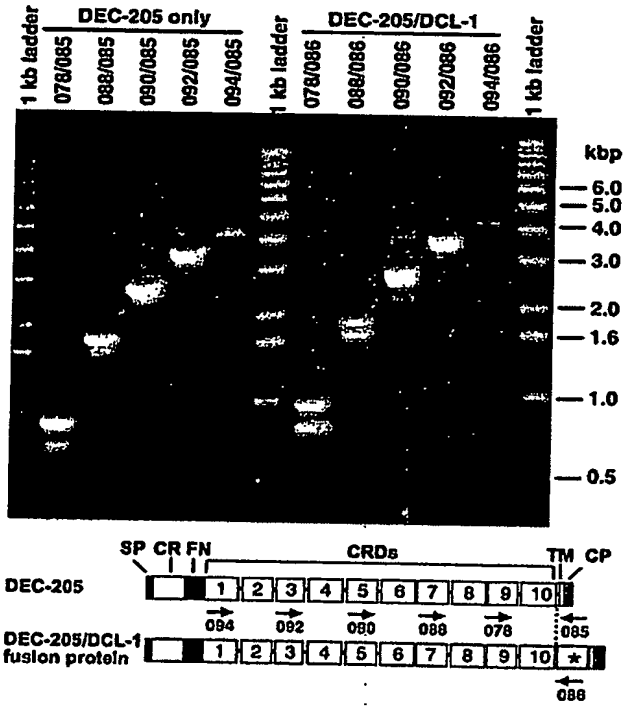


Figure 2

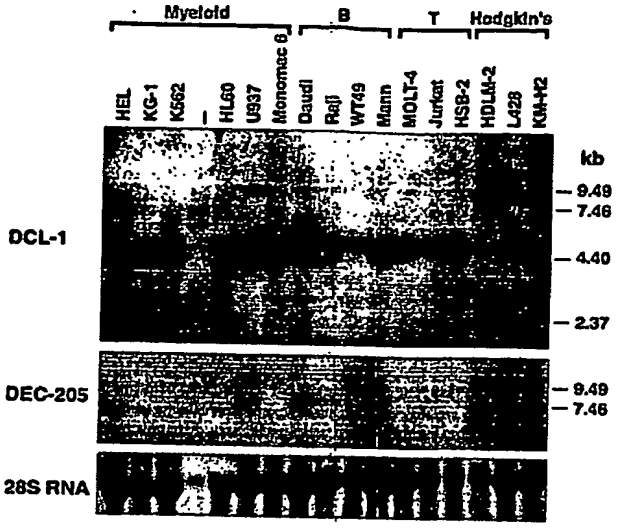
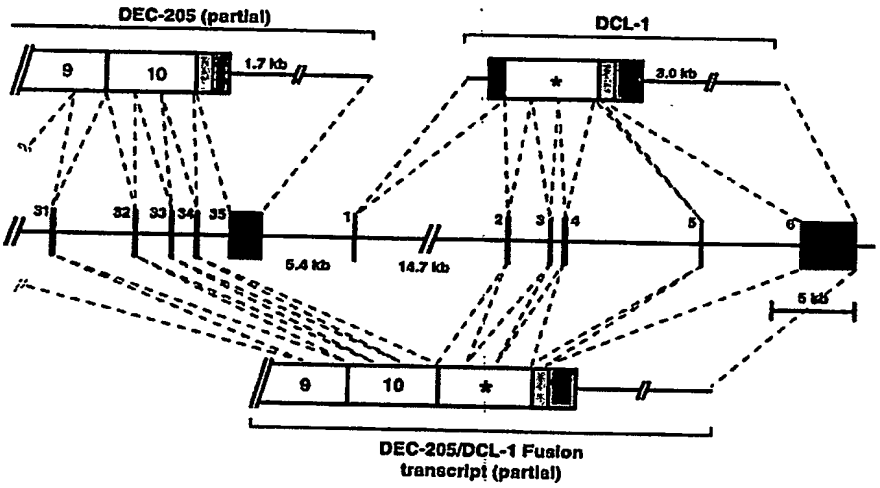


Figure 3



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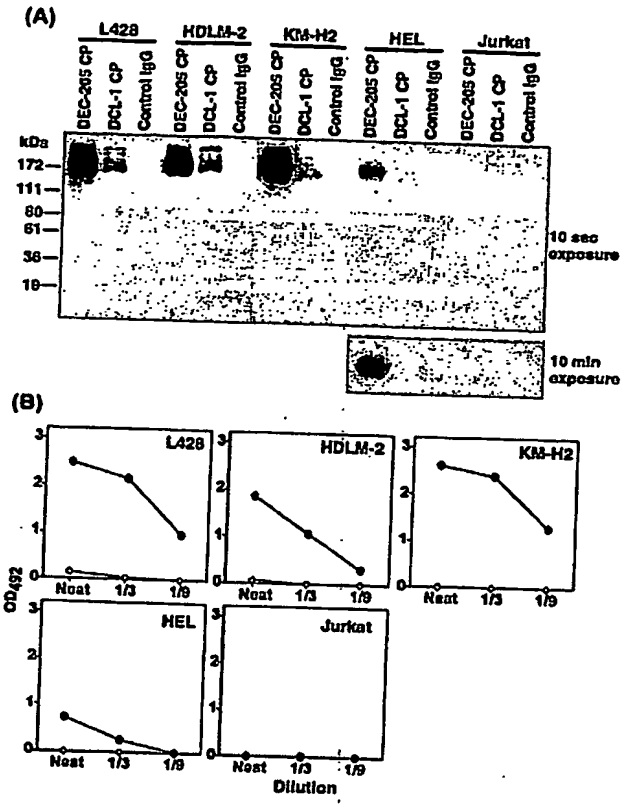
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19
10 sec exposure
10 min exposure
(B)
L428
HDLM-2
KM-H2
HEL
Jurkat
OD492
Neat
1/3
1/9
Dilution

Figure 5